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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07D 487/04, A61K 31/55
// (C07D 487/04, 253:00, 235:00)

A1

(11) International Publication Number: **WO 92/12154**

(43) International Publication Date: 23 July 1992 (23.07.92)

(21) International Application Number: PCT/JP91/01768

(22) International Filing Date: 26 December 1991 (26.12.91)

(30) Priority data:

9028217.9	31 December 1990 (31.12.90)	GB
9113017.9	17 June 1991 (17.06.91)	GB

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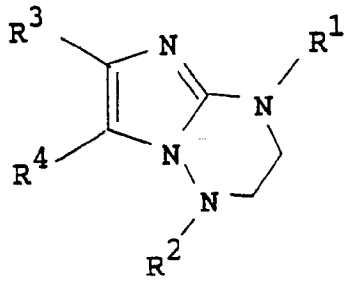
(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: IMIDAZOTRIAZINE DERIVATIVES



(I)

(57) Abstract

Imidazotriazine derivatives of formula (I), wherein R^1 is hydrogen, lower alkyl or acyl, R^2 is hydrogen, or acyl, R^3 is aryl which may have suitable substituent(s), etc., and R^4 is heterocyclic group which may have suitable substituent(s), heterocyclicalkyl, heterocyclicsulfinyl or heterocyclicthio with interleukin-1 (IL-1) and tumor necrosis factor (TNF) inhibitory activities.

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DESCRIPTION

IMIDAZOTRIAZINE DERIVATIVES

TECHNICAL FIELD

This invention relates to new imidazotriazine derivatives and pharmaceutically acceptable salts thereof which are useful as a medicament.

BACKGROUND ART

Some heterocyclic compounds having a strong inhibitory activity on the production of Interleukin-1 (IL-1) have been known as described, for example, in U.S. Patent 4,780,470, U.S. Patent 4,778,806 and U.S. Patent 4,794,114.

DISCLOSURE OF INVENTION

This invention relates to new imidazotriazine derivatives. More particularly, this invention relates to new imidazotriazine derivatives and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and a use of the same.

Accordingly, one object of this invention is to provide the new and useful imidazotriazine derivatives and pharmaceutically acceptable salts thereof which possess a strong inhibitory activity on the production of Interleukin-1 (IL-1) and a strong inhibitory activity on the production of tumor necrosis factor (TNF).

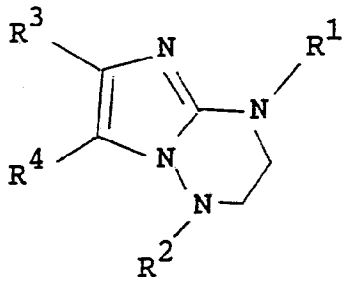
Another object of this invention is to provide processes for preparation of the imidazotriazine derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said imidazotriazine

derivatives or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said imidazotriazine derivatives or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and therapeutic treatment of IL-1 and TNF mediated diseases such as chronic inflammatory diseases, specific autoimmune diseases, sepsis-induced organ injury, and the like in human being and animals.

The object imidazotriazine derivatives of the present invention are novel and can be represented by the following general formula (I) :

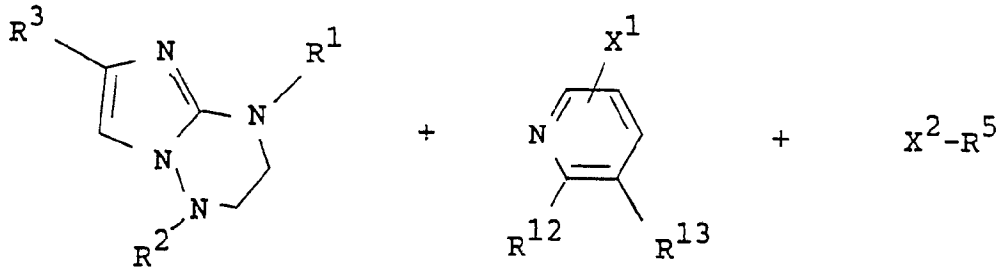


(I)

wherein R^1 is hydrogen, lower alkyl or acyl,
R^2 is hydrogen, or acyl,
R^3 is aryl which may have suitable substituent(s), or heterocyclic group which may have suitable substituent(s), and
R^4 is heterocyclic group which may have suitable substituent(s), heterocyclic(lower)alkyl, heterocyclicthio, or heterocyclicsulfinyl.

The object compound (I) of the present invention can be prepared by the following processes.

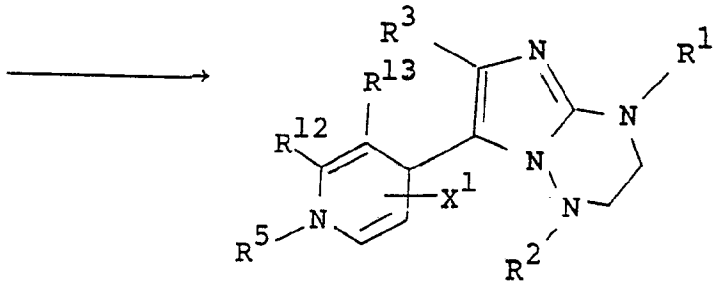
Process (1)



(II) or a salt thereof

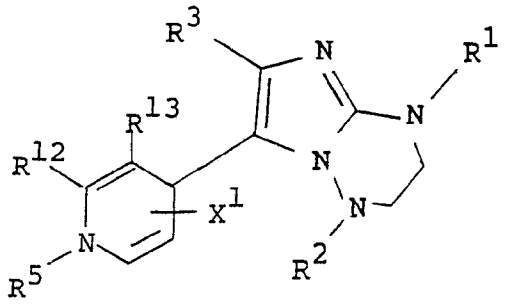
(III) or a salt thereof

(IV)



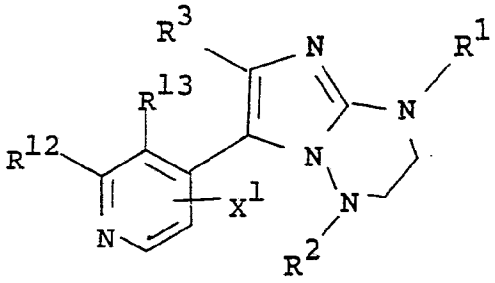
(Ia) or a salt thereof

Process (2)



oxidation

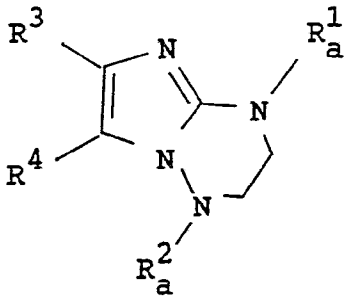
(Ia) or a salt thereof



(Ib)

or a salt thereof

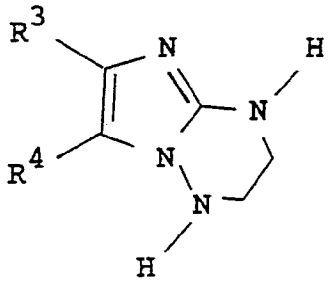
Process (3)



deacylation

(Ic)

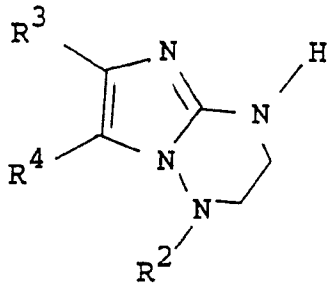
or a salt thereof



(Id)

or a salt thereof

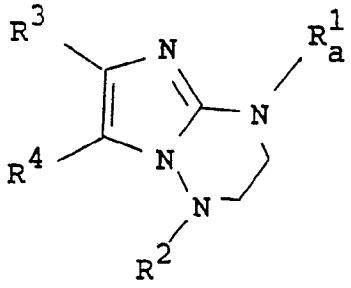
Process (4)



acylation

(Ie)

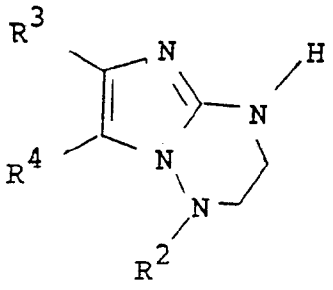
or a salt thereof



(If)

or a salt thereof

Process (5)

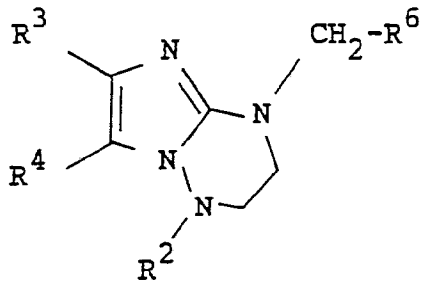


i) R^6 - CHO (V)

ii) reduction

(Ie)

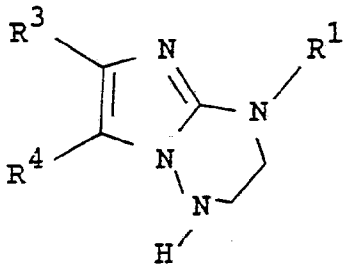
or a salt thereof



(Ig)

or a salt thereof

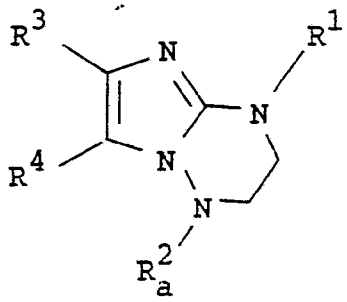
Process (6)



acylation

(Ih)

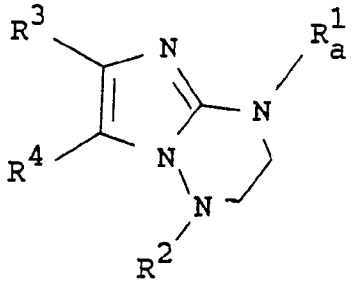
or a salt thereof



(Ii)

or a salt thereof

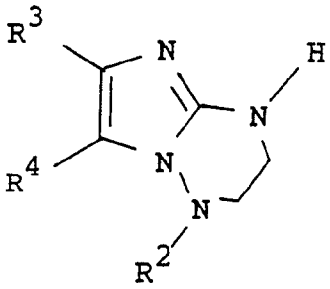
Process (7)



deacylation

(If)

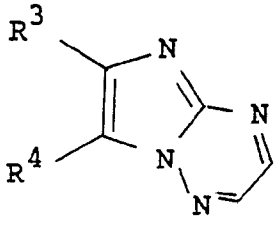
or a salt thereof



(Ie)

or a salt thereof

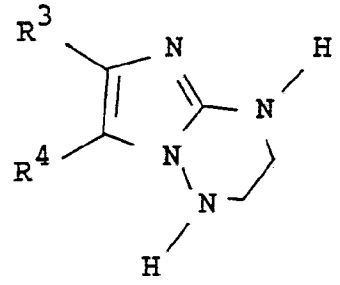
Process (8)



reduction

(X)

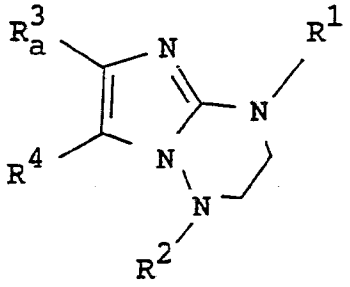
or a salt thereof



(Id)

or a salt thereof

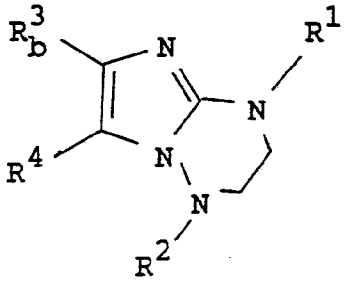
Process (9)



Elimination reaction of the carboxy protective group(s) ⟶

(Ij)

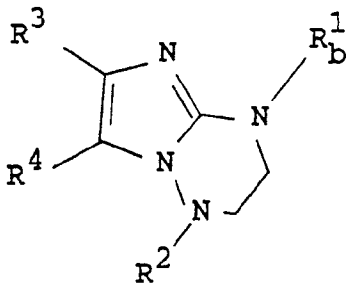
or a salt thereof



(Ik)

or a salt thereof

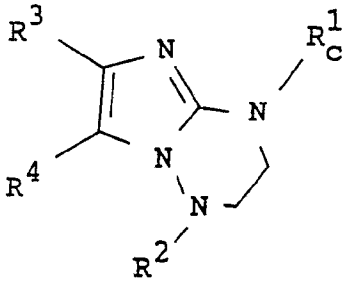
Process (10)



(Iℓ)

or a salt thereof

↓ Elimination reaction of the hydroxy protective group(s)

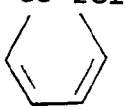


(Im)

or a salt thereof

wherein R^1, R^2, R^3 and R^4 are each as defined above,

R^{12} and R^{13} are each hydrogen, or

R^{12} and R^{13} are linked together to form a group of the formula :  ,

X^1 is an acid residue, carboxy or protected carboxy,

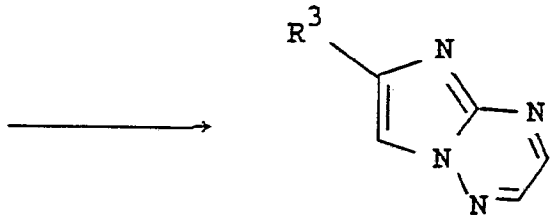
X^2 is an acid residue,
R^5 is protected carboxy,
$R^1_{a_6}$ and R^2_a are each acyl,
R^6 is hydrogen or C_1-C_5 alkyl,
$R^3_{a_3}$ is aryl having protected carboxy group(s),
R^3_b is aryl having carboxy group(s),
$R^1_{b_1}$ is acyl having protected hydroxy group(s), and
R^1_c is acyl having hydroxy group(s).

The starting compounds (II) and (X) can be prepared by the following Processes.

Process (A)

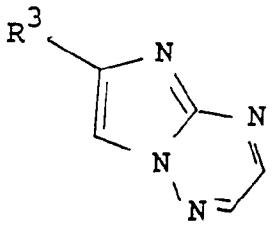
(VI)
or a salt thereof

(VII)
or a salt thereof



(VIII)
or a salt thereof

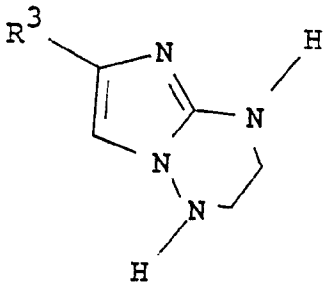
Process (B)



reduction

(VIII)

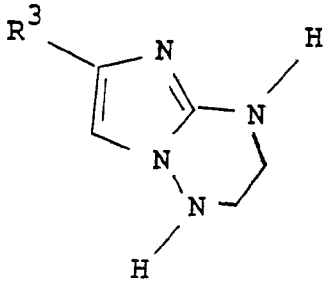
or a salt thereof



(IIa)

or a salt thereof

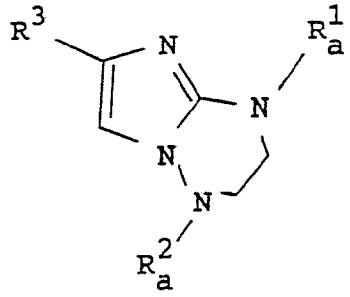
Process (C)



acylation

(IIa)

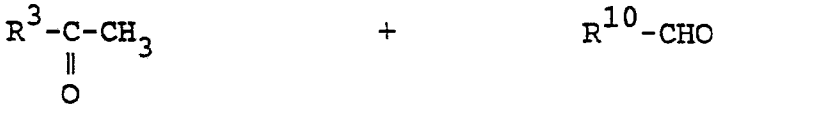
or a salt thereof



(IIb)

or a salt thereof

Process (D)



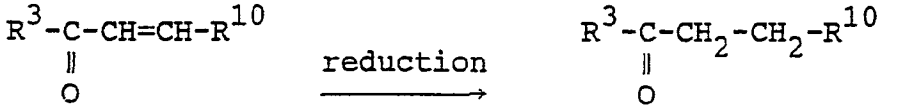
(XI) (XII)

or a salt thereof or a salt thereof

(XIII)

or a salt thereof

Process (E)



(XIII) (XIVa)

or a salt thereof or a salt thereof

Process (F)

R^{11} - SH

(XV)
or a salt thereof

R^3-CO-CH_2-X^3

(VI)
or a salt thereof

R^3-CO-CH_2-S-R^{11}

(XIVb)
or a salt thereof

Process (G)

R^4 - CH_3

(XVI)
or a salt thereof

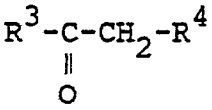
R^3-C(=O)-X^4

(XVII)
or a salt thereof

R^3-C(=O)-CH_2-R^4

(XIV)
or a salt thereof

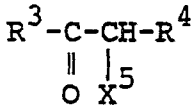
Process (H)



(XIV)

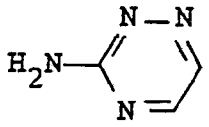
or a salt thereof

① halogenation



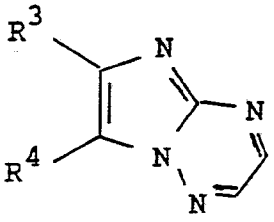
(XVIII)

or a salt thereof

② 

(VII)

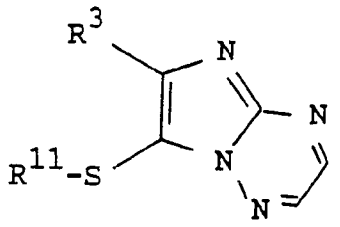
or a salt thereof



(X)

or a salt thereof

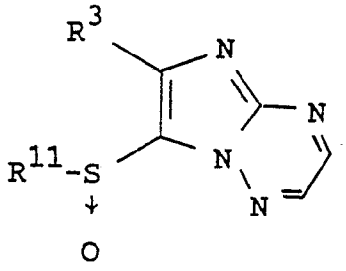
Process (I)



(Xa)

or a salt thereof

↓ oxidation



(Xb)

or a salt thereof

wherein R^1_a, R^2_a, R^3 and R^4 are each as defined above,
R^{10} and R^{11} are each heterocyclic group,
X^3 and X^4 are each an acid residue, and
X^5 is halogen.

Suitable pharmaceutically acceptable salts of the object compound (I) are conventional non-toxic salts and may include e.g. a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g. sodium salt, potassium salt,

etc.), an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.) an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g. triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable example and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

The term "higher" is used to intend a group having 7 to 20, preferably 7 to 12, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the term "heterocyclic(lower)alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl, hexyl, and the like, in which more preferable example may be C_1-C_4 alkyl.

Suitable "acyl" may include carbamoyl, aliphatic acyl group and acyl group containing an aromatic ring, which is referred to as aromatic acyl, or heterocyclic ring, which is referred to as heterocyclic acyl. This acyl group may be derived, for example, from an organic carboxylic, an organic carbonic, an organic sulfuric, an organic sulfonic

and an organic carbamic acids.

Suitable example of said acyl may be illustrated as follows :-

Carbamoyl;

Alliphatic acyl such as lower or higher alkanoyl (e.g. formyl, acetyl, propanoyl, butanoyl, 2-methylpropanoyl, pentanoyl, 2,2-dimethylpropanoyl, hexanoyl, heptanoyl, octanoyl, nonanoyl, decanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, heptadecanoyl, octadecanoyl, nonadecanoyl, icosanoyl, etc.); lower or higher alkoxycarbonyl (e.g. methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, t-pentyloxycarbonyl, heptyloxycarbonyl, etc.);

lower or higher cycloalkylcarbonyl (e.g. cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohenylcarbonyl, etc.); lower or higher alkylsulfonyl (e.g. methylsulfonyl, ethylsulfonyl, etc.);

lower or higher alkoxysulfonyl (e.g. methoxysulfonyl, ethoxysulfonyl, etc.); or the like;

Aromatic acyl such as

aroyl (e.g. benzoyl, toluoyl, naphthoyl, etc.);

ar(lower)alkanoyl [e.g. phenyl(lower)alkanoyl (e.g. phenylacetyl, phenylpropanoyl, phenylbutanoyl, phenylisobutylyl, phenylpentanoyl, phenylhexanoyl, etc.), naphthyl(lower)alkanoyl (e.g. naphthylacetyl, naphthylpropanoyl, naphthylbutanoyl, etc.), etc.];

ar(lower)alkenoyl [e.g. phenyl(lower)alkenoyl (e.g. phenylpropenoyl, phenylbutenoyl, phenylmethacryloyl, phenylpentenoyl, phenylhexenoyl, etc.), naphthyl(lower)alkenoyl (e.g. naphthylpropenoyl, naphthylbutenoyl, naphthylpentenoyl, etc.), etc.];

ar(lower)alkoxycarbonyl [e.g. phenyl(lower)alkoxy-carbonyl (e.g. benzyloxycarbonyl, etc.), etc.];

aryloxycarbonyl (e.g. phenoxycarbonyl, naphthyloxy-carbonyl, etc.);
aryloxy(lower)alkanoyl (e.g. phenoxyacetyl, phenoxypropionyl, etc.);
arylcarbamoyl (e.g. phenylcarbamoyl, etc.);
arylthiocarbamoyl (e.g. phenylthiocarbamoyl, etc.);
arylglyoxyloyl (e.g. phenylglyoxyloyl, naphthylglyoxyloyl, etc.);
arylsulfonyl (e.g. phenylsulfonyl, naphthylsulfonyl, etc.); or the like;

Heterocyclic acyl such as
heterocycliccarbonyl;
heterocyclic (lower)alkanoyl (e.g. thienylacetyl, thienylpropanoyl, thienylbutanoyl, thienylpentanoyl, thienylhexanoyl, thiazolylacetyl, thiadiazolylacetyl, tetrazolylacetyl, etc.);
heterocyclic(lower)alkenoyl (e.g. heterocyclicpropenoyl, heterocyclicbutenoyl, heterocyclicpentenoyl, heterocyclichexenoyl, etc.);
heterocyclicglyoxyloyl (e.g. thiazolylglyoxyloyl, thienylglyoxyloyl, etc.); or the like.

Suitable "heterocyclic group" and heterocyclic moiety in the terms "heterocycliccarbonyl", "heterocyclic(lower)alkanoyl", heterocyclic(lower)alkenoyl and "heterocyclicglyoxyloyl" means saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.
And, especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered more preferably 5 or 6-membered heteromonocyclic group containing 1 to 4-nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl and its N-oxide, dihydropyridyl, pyrimidyl, pyrazinyl, pyridazinyl,

triazolyl (e.g. 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example pyrrolidinyl, imidazolidinyl, piperidino, piperazinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, dihydroquinolyl, isoquinolyl, indazolyl, benzotriazolyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.) etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered)heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g. 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;
saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolidinyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2

sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 to 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;
unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example benzothienyl (e.g. benzo[b]thienyl, etc.), benzodithiinyl, etc.;
unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc. and the like.

The acyl moiety as stated above may have one to five, same or different, suitable substituent(s) such as halogen (e.g. fluorine, chlorine, bromine or iodine), lower alkyl (e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, etc.);
lower alkoxy (e.g. methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, t-butoxy, pentyloxy, hexyloxy, etc.), hydroxy, carboxy, protected hydroxy, protected carboxy, mono(or di or tri)halo(lower)alkyl, N,N-di(lower)-alkylamino (e.g. N,N-dimethylamino, N,N-diethylamino, N,N-dipropylamino, N,N-dibutylamino, N,N-dipentylamino, N,N-dihexylamino, N-methyl-N-ethylamino, N-methyl-N-butylamino, etc.), or the like.

Suitable "mono(or di or tri)halo(lower)alkyl" means straight or branched lower alkyl having one to three halogen (e.g. chlorine, bromine, iodine, fluorine) such as chloromethyl, fluoromethyl, dichloromethyl, dibromomethyl, diiodomethyl, difluoromethyl, trifluoromethyl,

chloroethyl, chlorofluoroethyl, difluoroethyl, trifluoroethyl, chloropropyl, difluoropropyl, trichlorobutyl, chloropentyl, chlorohexyl, and the like.

Suitable "protected hydroxy" may include acyloxy and the like.

Suitable "acyl moiety" in the term "acyloxy" can be referred to the ones as exemplified above.

Suitable "protected carboxy" may include esterified carboxy and the like.

Suitable example of the ester moiety of an esterified carboxy may be the ones such as lower alkyl ester (e.g. methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, tert-butyl ester, pentyl ester, hexyl ester, 1-cyclopropylethyl ester, etc.) which may have at least one suitable substituent(s), for example, lower alkanoyloxy(lower)alkyl ester [e.g. acetoxymethyl ester, propionyloxymethyl ester, butyryloxymethyl ester, valeryloxymethyl ester, pivaloyloxymethyl ester, hexanoyloxymethyl ester, 1(or 2)-acetoxyethyl ester, 1(or 2 or 3)-acetoxypropyl ester 1(or 2 or 3 or 4)-acetoxybutyl ester, 1(or 2)-propionyloxyethyl ester, 1(or 2 or 3)-propionyloxypropyl ester, 1(or 2)-butyryloxyethyl ester, 1(or 2)-isobutyryloxyethyl ester, 1(or 2)-pivaloyloxyethyl ester, 1(or 2)-hexanoyloxyethyl ester, isobutyryloxymethyl ester, 2-ethylbutyryloxymethyl ester, 3,3-dimethylbutyryloxymethyl ester, 1(or 2)-pentanoyloxyethyl ester, etc.], lower alkanesulfonyl(lower)alkyl ester (e.g. 2-mesylethyl ester, etc.), mono(or di or tri)-halo(lower)alkyl ester (e.g. 2-iodoethyl ester, 2,2,2-trichloroethyl ester, etc.), lower alkoxycarbonyloxy(lower)alkyl ester (e.g. methoxy-carbonyloxymethyl ester, ethoxycarbonyloxymethyl ester, 2-methoxycarbonyloxyethyl ester, 1-ethoxycarbonyloxyethyl ester, 1-isopropoxycarbonyloxyethyl ester, etc.),

phthalidylidene(lower)alkyl ester, or (5-lower alkyl 2-oxo-1,3-dioxol-4-yl)(lower)alkyl ester [e.g. (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-ethyl-2-oxo-1,3-dioxol-4-yl)methyl ester, (5-propyl-2-oxo-1,3-dioxol-4-yl)ethyl ester, etc.];
lower alkenyl ester (e.g. vinyl ester, allyl ester, etc.);
lower alkynyl ester (e.g. ethynyl ester, propynyl ester, etc.);
ar(lower)alkyl ester which may have at least one suitable substituent(s) such as mono(or di or tri)phenyl(lower)alkyl ester which may have at least one suitable substituent(s) (e.g. benzyl ester, 4-methoxybenzyl ester, 4-nitrobenzyl ester, phenethyl ester, trityl ester, benzhydryl ester, bis(methoxyphenyl)methyl ester, 3,4-dimethoxybenzyl ester, 4-hydroxy-3,5-di-tert-butylbenzyl ester, etc.);
aryl ester which may have at least one suitable substituent(s) (e.g. phenyl ester, 4-chlorophenyl ester, tolyl ester, tert-butylphenyl ester, xylyl ester, mesityl ester, cumenyl ester, etc.);
phthalidyl ester; and the like.

Suitable "aryl" may include phenyl, naphthyl and the like.

Suitable "acid residue" may include halogen [e.g. fluorine, chlorine, bromine and iodine] and the like.

Suitable "C_1-C_5 alkyl" may include straight or branched one such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, pentyl and the like.

Suitable "substituent" in the term "aryl which may have suitable substituent(s)" may include halogen, protected carboxy, mono(or di or tri)halo(lower)alkyl, carboxy, hydroxy(lower)alkyl wherein lower alkyl moiety can be referred to the ones as exemplified above, aryl which may have one or two halogen, or the like.

Suitable "substituent" in the term "heterocyclic

group which may have suitable substituent(s)" may include an acid residue, carboxy, lower alkyl, protected carboxy, or the like.

Suitable "heterocyclic group" in the terms "heterocyclic(lower)alkyl", "heterocyclicthio" and "heterocyclicsulfinyl" can be referred to the ones as exemplified above.

The processes for preparing the object and starting compounds are explained in detail in the following.

Process (1)

The compound (Ia) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof and the compound (IV).

The reaction is usually carried out in a conventional solvent such as alcohol (e.g., methanol, ethanol, etc.), tetrahydrofuran, N,N-dimethylformamide, dichloromethane, acetic acid, or any other solvent which does not adversely influence the reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

Process (2)

The compound (Ib) or a salt thereof can be prepared by subjecting the compound (Ia) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable of oxidizing N-protected carboxy substituted dihydropyridine or dihydroquinoline to pyridine or quinoline, and suitable oxidizing reagent may be sulfur, oxygen, alkali metal alkoxide (e.g., potassium t-butoxide, etc.), or the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol,

isopropyl alcohol, t-butyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, chloroform, dimethyl acetamide, decalin, tetralin, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (3)

The compound (Id) or a salt thereof can be prepared by subjecting the compound (Ic) or a salt thereof to deacylation reaction. Suitable method of this reaction may include conventional one such as hydrolysis, reduction and the like.

(i) For Hydrolysis :

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

Suitable base may include an inorganic base and an organic base such as an alkali metal [e.g. sodium, potassium, etc.], the hydroxide or carbonate or bicarbonate thereof, alkali metal lower alkoxide (e.g. sodium methoxide, sodium ethoxide, etc.], hydrides [e.g. lithium aluminum hydride, etc.], trialkylamine [e.g. trimethylamine, triethylamine, etc.], picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid may include an organic acid [e.g. formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.] and an inorganic acid [e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.].

The elimination using Lewis acid such as trihaloacetic acid [e.g. trichloroacetic acid, trifluoroacetic acid, etc.] or the like is preferably carried out in the presence of cation trapping agents [e.g. anisole, phenol, etc.].

The reaction is usually carried out in a solvent such as water, an alcohol [e.g. methanol, ethanol, etc.], methylene chloride, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely influence the reaction. A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is usually carried out under cooling to warming.

(ii) For reduction :

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt, etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper, etc.) and the

like. The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, methanol, ethanol, propanol, N,N-dimethylformamide, tetrahydrofuran, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The present invention includes, within the scope of the invention, the cases that the protected carboxy group in R^3 is transformed into a carboxy group or hydroxymethyl during the reaction and that the protected carboxy group in R^4 is transformed into a carboxy group during the reaction.

Process (4)

The compound (If) or a salt thereof can be prepared by subjecting the compound (Ie) or a salt thereof to acylation reaction.

Suitable acylating agent to be used in the present acylation reaction may include the compound of the formula:

$$R_a^1 - OH \qquad (IX)$$

(wherein R_a^1 is acyl)

or its reactive derivative or a salt thereof.

Suitable reactive derivative of the compound (IX) may include an acid halide, an acid anhydride, an activated amide, an activated ester, isocyanate, and the like. The suitable example may be an acid chloride, an acid azide;

a mixed acid anhydride with an acid such as substituted phosphoric acid (e.g. dialkylphosphoric acid, phenylphosphoric acid, diphenylphosphoric acid, dibenzylphosphoric acid, halogenated phosphoric acid, etc.), dialkylphosphorous acid, sulfurous acid, thiosulfuric acid, alkanesulfonic acid (e.g. methanesulfonic acid, ethanesulfonic acid, etc.), sulfuric acid, alkylcarbonic acid, aliphatic carboxylic acid (e.g. pivalic acid, pentanoic acid, isopentanoic acid, 2-ethylbutyric acid or trichloroacetic acid, etc.) or aromatic carboxylic acid (e.g. benzoic acid, etc.); a symmetrical acid anhydride; a cyclic acid anhydride; an activated amide with imidazole, 4-substituted imidazole, dimethylpyrazole, triazole or tetrazole; or an activated ester (e.g. cyanomethyl ester, methoxymethyl ester, dimethyliminomethyl [$(CH_3)_2\overset{+}{N}=CH-$] ester, vinyl ester, propargyl ester, p-nitrophenyl ester, 2,4-dinitrophenyl ester, trichlorophenyl ester, pentachlorophenyl ester, mesylphenyl ester, phenylazophenyl ester, phenyl thioester, p-nitrophenyl thioester, p-cresyl thioester, carboxymethyl thioester, pyranyl ester, pyridyl ester, piperidyl ester, 8-quinolyl thioester, etc.), or an ester with a N-hydroxy compound (e.g. N,N-dimethylhydroxylamine, 1-hydroxy-2-(1H)-pyridone, N-hydroxysuccinimide, N-hydroxybenzotriazole, N-hydroxyphthalimide, 1-hydroxy-6-chloro-1H-benzotriazole, etc.); substituted or unsubstituted aryl isocyanate; substituted or unsubstituted aryl isothiocyanate; substituted or unsubstituted lower alkyl isocyanate; and the like. These reactive derivatives can optionally be selected from them according to the kind of the compound (IX) to be used.

The reaction is usually carried out in a conventional solvent such as water, acetone, dioxane, acetonitrile, chloroform, methylene chloride, ethylene chloride,

tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, pyridine or any other organic solvents which do not adversely influence the reaction. These conventional solvents may also be used in a mixture with water.

When the compound (IX) is used in free acid form or its salt form in the reaction, the reaction is preferably carried out in the presence of a conventional condensing agent such as N,N'-dicyclohexylcarbodiimide; N-cyclohexyl-N'-morpholinoethylcarbodiimide; N-cyclohexyl-N'-(4-diethylaminocyclohexyl)carbodiimide; N,N'-diethylcarbodiimide, N,N'-diisopropylcarbodiimide; N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide; N,N-carbonylbis-(2-methylimidazole); pentamethyleneketene-N-cyclohexylimine, diphenylketene-N-cyclohexylimine; ethoxyacetylene; 1-alkoxy-1-chloroethylene; trialkyl phosphite; ethyl polyphosphate; isopropyl polyphosphate; phosphorus oxychloride (phosphoryl chloride); phosphorus trichloride; thionyl chloride; oxalyl chloride; triphenylphosphine; 2-ethyl-7-hydroxybenzisoxazolium salt; 2-ethyl-5-(m-sulfophenyl)isoxazolium.hydroxide intra-molecular salt; 1-(p-chlorobenzenesulfonyloxy)-6-chloro-1H-benzotriazole; so-called Vilsmeier reagent prepared by the reaction of N,N-dimethylformamide with thionyl chloride, phosgene, phosphorus oxychloride, etc.; or the like.

The reaction may also be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine, pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like. The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

The present invention includes, within the scope of the invention, the case that hydrogen in R^2 is transformed

into a acyl group during the reaction.

Process (5)

The compound (Ig) or a salt thereof can be prepared by reacting the compound (Ie) or a salt thereof with the compound (V) and then by subjecting the resultant compound to reduction reaction.

Reduction is carried out in a conventional manner, including chemical reduction and catalytic reduction.

Suitable reducing agents to be used in chemical reduction are hydrides (e.g. hydrogen iodide, hydrogen sulfide, lithium aluminum hydride, sodium borohydride, sodium cyanoborohydride, etc.) or a combination of a metal (e.g. tin, zinc, iron, etc.) or metallic compound (e.g. chromium chloride, chromium acetate, etc.) and an organic or inorganic acid (e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.).

Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalysts (e.g. platinum plate, spongy platinum, platinum black, colloidal platinum, platinum oxide, platinum wire, etc.), palladium catalysts (e.g. spongy palladium, palladium black, palladium oxide, palladium on carbon, colloidal palladium, palladium on barium sulfate, palladium on barium carbonate, etc.), nickel catalysts (e.g. reduced nickel, nickel oxide, Raney nickel, etc.), cobalt catalysts (e.g. reduced cobalt, Raney cobalt,etc.), iron catalysts (e.g. reduced iron, Raney iron, etc.), copper catalysts (e.g. reduced copper, Raney copper, Ullman copper etc.) and the like.

The reaction is usually carried out in a solvent such as water, alcohol (e.g. methanol, ethanol, etc.), N,N-dimethylformamide, tetrahydrofuran, a mixture thereof or any other solvent which does not adversely affect the

reaction.

Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent.

The reaction temperature of this reaction is not critical and the reaction is usually carried out under cooling to heating.

Process (6)

The compound (Ii) or a salt thereof can be prepared by subjecting the compound (Ih) or a salt thereof to acylation reaction. This reaction can be carried out in a similar manner to that of the aforementioned Process (4), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (4).

Process (7)

The compound (Ie) or a salt thereof can be prepared by subjecting the compound (If) or a salt thereof to deacylation reaction. This reaction can be carried out in a similar manner to that of the aforementioned Process (3), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (3).

Process (8)

The compound (Id) or a salt thereof can be prepared by subjecting the compound (X) or a salt thereof to reduction reaction. This reduction can be carried out in a similar manner to that of the aforementioned Process (5), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (5).

Process (9)

The compound (Ik) or a salt thereof can be prepared by subjecting the compound (Ij) or a salt thereof to elimination reaction of the carboxy protective group(s).

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

This reaction can be carried out in a similar manner to that of the aforementioned Process (3), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (3).

Process (10)

The compound (Im) or a salt thereof can be prepared by reacting the compound (Iℓ) or a salt thereof to elimination reaction of the hydroxy protective group(s).

This reaction is carried out in accordance with a conventional method such as hydrolysis, reduction or the like.

This reaction can be carried out in a similar manner to that of the aforementioned Process (3) and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (3).

Process (A)

The compound (VIII) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof.

This reaction is usually carried out in a solvent such as alcohol (e.g., methanol, ethanol, etc.), benzene, N,N-dimethylformamide, tetrahydrofuran, methylene chloride, ethylene chloride, chloroform, diethyl ether or any other solvent which does not adversely affect the

reaction.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Process (B)

The compound (IIa) or a salt thereof can be prepared by subjecting the compound (VIII) or a salt thereof to reduction. This reduction can be carried out in a similar manner to that of the aforementioned Process (5), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (5).

Process (C)

The compound (IIb) or a salt thereof can be prepared by subjecting the compound (IIa) or a salt thereof to acylation reaction. This reaction can be carried out in a similar manner to that of the aforementioned Process (4), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (4).

Process (D)

The compound (XIII) or a salt thereof can be prepared by reacting the compound (XI) or a salt thereof with the compound (XII) or a salt thereof.

This reaction can be carried out in accordance with the method disclosed in the Preparation 4 described later or a similar manner thereto.

Process (E)

The compound (XIVa) or a salt thereof can be prepared by subjecting the compound (XIII) or a salt thereof to reduction reaction. This reduction can be carried out in a similar manner to that of the aforementioned

Process (5), and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of the Process (5).

Process (F)

The compound (XIVb) or a salt thereof can be prepared by reacting the compound (XV) or a salt thereof with the compound (VI) or a salt thereof.

This reaction can be carried out in accordance with the method disclosed in the Preparation 7 described later or a similar manner thereto.

Process (G)

The compound (XIV) or a salt thereof can be prepared by reacting the compound (XVI) or a salt thereof with the compound (XVII) or a salt thereof.

This reaction can be carried out in accordance with the method disclosed in the Preparation 8 described later or a similar manner thereto.

Process (H)-(1)

The compound (XVIII) or a salt thereof can be prepared by subjecting the compound (XIV) or a salt thereof to halogenation reaction.

This reaction can be carried out in accordance with the method disclosed in the Preparation 6 and 9-(1) described later or a similar manner thereto.

Process (H)-(2)

The compound (X) or a salt thereof can be prepared by reacting the compound (XVIII) or a salt thereof with the compound (VII) or a salt thereof.

This reaction can be carried out in a similar manner to that of the aforementioned Process (A), and therefore the reagents to be used and the reaction conditions (e.g.,

solvent, reaction temperature, etc.) can be referred to those of the Process (A).

Process (I)

The compound (Xb) or a salt thereof can be prepared by subjecting the compound (Xa) or a salt thereof to oxidation reaction.

Oxidation is carried out in a conventional manner, which is capable of sulfur atom(s) to oxidized sulfur atom(s), and suitable oxidizing reagent may be oxygen acid such as periodate (e.g. sodium periodate, etc.), peroxy acid such as peroxybenzoic acids (e.g. peroxybenzoic acid, m-chloroperoxybenzoic acid, etc.), and the like.

The reaction is usually carried out in a conventional solvent such as water, alcohol (e.g., methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, dichloromethane, chloroform, N,N-dimethyl acetamide, N,N-dimethylformamide or any other organic solvent which does not adversely influence the reaction. Among these solvents, hydrophilic solvents may be used in a mixture with water.

The reaction temperature is not critical and the reaction is usually carried out under cooling to heating.

Suitable salts of the object and starting compounds and their reactive derivatives in Processes (1)~(10) and (A)~(I) can be referred to the ones as exemplified for the compound (I).

The new imidazotriazine derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention possess a strong inhibitory activity on the production of Interleukin-1 (IL-1) and a strong inhibitory activity on the production of tumor necrosis factor (TNF), and therefore are useful as an inhibitor on the production of Interleukin-1 (IL-1) and an inhibitor on the production of tumor necrosis factor (TNF).

Accordingly, the new imidazotriazine derivatives (I) and a pharmaceutically acceptable salt thereof can be used for prophylactic and therapeutic treatment of IL-1 and TNF mediated diseases such as chronic inflammatory diseases (e.g. rheumatoid arthritis, osteoarthritis, etc.) osteoporosis, rejection by transplantation, asthma, endotoxin shock, specific autoimmune diseases [e.g. ankylosing spondylitis, autoimmune hematological disorders (e.g. hemolyticodo anaemia, aplastic anaemia, pure red cell anaemia, idiopathic thrombocytopenia, etc.), systemic lupus erythematosus, polychondritis, scleroderma, Wegener granulamotosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, idiopathic sprue, autoimmune inflammatory bowel disease (e.g. ulcerative colitis, Crohn's disease, etc.), endocrine opthalmopathy, Grave's disease, sarcoidosis, multiple scleosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), Reiter's syndrome, non infection uveitis, autoimmune keratitis (e.g. keratoconjuntivitis sicca, vernal keratoconjunctivitis, etc.), interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis {e.g. nephrotic syndrome (e.g. idiopathic nephrotic syndrome, minimal change nephropathy, etc.), etc.}, etc.], cancer cachexia, AIDS cachexia and the like.

In order to show the utilities of the imidazotriazine derivatives (I) and a pharmaceutically acceptable salt thereof of the present invention, pharmacological test data of the representative compound of the imidazotriazine derivatives (I) are illustrated in the following.

The expressions of "Example 3-(1)", "Example 3-(4)" and "Example 3-(5)" in the following test mean the compounds prepared in Example 3-(1), 3-(4) and 3-(5) respectively.

(a) Inhibitory activity on the production of Interleukin-1 (IL-1)

1. Test method

Purified human peripheral blood monocyte were stimulated with bacterial lipopolysaccharide (1 μg/10^4 cells) in the absence or presence of appropriately diluted test compounds for 2 days at 37°C in a humidified 5% CO_2 atmosphere. Culture supernatants were tested for IL-1 ELISA assay.

Test compounds were dissolved in absolute DMSO (dimethyl sulfoxide) to achieve 10 mM stock solutions and were subsequently diluted in serum free RPMI1640.

IL-1 levels were quantified by a commercial ELISA kit (Ohtuka assay, Japan) using a sandwitch technique. The sensitivity levels for the detection of IL-1β were 20 pg/ml.

The inhibitory concentration that caused a 50% inhibition (IC_{50}) was calculated by regression analysis of the dose-response data.

2. Test result

Test compound	IC_{50} (M)
Example 3-(4)	1.3×10^{-7}
Example 3-(5)	1.5×10^{-7}

(b) Inhibitory activity on the production of tumor necrosis factor (TNF)

1. Test method

Purified human peripheral blood monocyte were stimulated with bacterial lipopolysaccharide (1 μg/10^4 cells) in the absence or presence of appropriately diluted test compounds for 2 days at 37°C in a humidified 5% CO_2 atmosphere. Culture supernatants were tested for TNF ELISA assay.

TNF levels were quantified by a commercial ELISA kit (Endogen, Inc. USA) using a sandwitch technique. The sensitivity levels for the detection of TNF were 12 pg/ml.

The inhibitory concentration that caused a 50% inhibition (IC_{50}) was calculated by regression analysis of the dose-response data.

2. Test result

Test compound	IC_{50} (M)
Example 3-(1)	1.89×10^{-1}

For therapeutic administration, the object compounds (I) of the present invention and pharmaceutically acceptable salts thereof are used in a form of the conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration. The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee or suppository, or in a liquid form such as solution, suspension or emulsion for injection, ingestion, eye drops, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent,

wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered with a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

Preferred embodiments of the object compound (I) are as follows.

R^1 is hydrogen, lower alkyl, lower or higher alkanoyl which may have one to five suitable substituent(s) [more preferably lower or higher alkanoyl which may have one to five substituent(s) selected from the group consisting of halogen, lower alkoxy and N,N-di(lower)alkylamino, most preferably C_1-C_{10} alkanoyl which may have one to five substituent(s) selected from the group consisting of halogen, lower alkoxy and N,N-di(lower)alkylamino], carbamoyl which may have one or two suitable substituent(s) [more preferably mono(or di)lower alkylcarbamoyl], lower alkylsulfonyl which may have one to three suitable substituent(s) [more preferably lower alkylsulfonyl which may have one to three halogen], arylsulfonyl which may have one to three suitable substituent(s) [more preferably arylsulfonyl which may have mono(or di or tri)halo(lower)alkyl, most preferably phenylsulfonyl which may have mono(or di or tri)halo(lower)alkyl], arylcarbonyl which may have one to three suitable substituent(s) [more preferably arylcarbonyl which may have one or two substituent(s) selected from the group consisting of carboxy and protected carboxy,

most preferably phenylcarbonyl which may have carboxy or protected carboxy], cyclo(lower)alkylcarbonyl [more preferably cyclo(C_5-C_6)alkylcarbonyl], ar(lower)alkanoyl which may have one to three suitable substituent(s) [more preferably ar(lower)alkanoyl which may have one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, hydroxy and protected hydroxy, most preferably phenyl(lower)-alkenoyl which may have one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, hydroxy and protected hydroxy], ar(lower)alkanoyl which may have one to three suitable substituent(s) [more preferably ar(lower)alkanoyl which may have one or two substituent(s) selected from the group consisting of lower alkoxy and halogen, most preferably phenyl(lower)alkanoyl which may have one or two substituent(s) selected from the group consisting of lower alkoxy and halogen], or heterocycliccarbonyl [more preferably unsaturated 5 or 6-membered heteromonocycliccarbonyl in which heteromonocyclic group contains 1 to 4 nitrogen atom(s), saturated 5 or 6-membered heteromonocyclic carbonyl in which heteromonocyclic group contains 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), or unsaturated 5 or 6-membered heteromonocycliccarbonyl in which heteromonocyclic group contains 1 to 2 sulfur atom(s), most preferably pyridylcarbonyl morpholinylcarbonyl or thienylcarbonyl],

R^2 is hydrogen,

lower or higher alkanoyl [more preferably lower alkanoyl],

carbamoyl which may have one or two suitable substituent(s) [more preferably mono(or di)lower-

alkylcarbamoyl], or lower alkylsulfonyl,

R^3 is aryl which may have one to three substituent(s) selected from the group consisting of halogen, mono(or di or tri)halo(lower)alkyl, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, carboxy, protected carboxy and mono(or di or tri)haloaryl [more preferably aryl which may have one or two substituent(s) selected from the group consisting of halogen, mono(or di or tri)halo(lower)alkyl, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, carboxy, protected carboxy and mono(or di or tri)haloaryl, most preferably mono(or di or tri)halophenyl, mono(or di or tri)halonaphthyl, mono(or di or tri)halo(lower)alkylphenyl, hydroxy(lower)alkylphenyl, carboxyphenyl, protected carboxyphenyl, or mono(or di or tri)halobiphenylyl], heterocyclic group which may have one to three suitable substituent(s) [more preferably unsaturated 5 or 6-membered heteronomoncyclic group containing 1 to 2 sulfur atom(s) which may have one or two substituent(s) selected from the group consisting of lower alkyl and halogen, or unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) which may have lower alkyl, most preferably thienyl which may have lower alkyl or halogen, or benzothienyl which may have lower alkyl],

R^4 is heterocyclic group [more preferably unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) or unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), most preferably dihydropyridyl, pyridyl, quinolyl, dihydroquinolyl or imidazolyl] which may have one to three (more preferably one or two substituent(s)

selected from the group consisting of protected carboxy, carboxy, halogen and lower alkyl,
unsaturated 5 or 6-membered heteromonocyclic (lower)alkyl in which heteromonocyclic group contains 1 to 4 nitrogen atom(s) [more preferably pyridyl(lower)alkyl],
unsaturated 5 or 6-membered heteromonocyclicthio in which heteromonocyclic group contains 1 to 4 nitrogen atom(s) [more preferably pyridylthio], or
unsaturated 5 or 6-membered heteromonocyclicsulfinyl in which heteromonocyclic group contains 1 to 4 nitrogen atom(s) [more preferably pyridylsulfinyl].

The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

(1) A mixture of 3-amino-1,2,4-triazine (4.8 g) and 2-bromo-4'-fluoroacetophenone (5.43 g) in ethanol (40 ml) was heated under reflux for one hour. After cooling, the reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane (160 ml) and methanol (40 ml). The solution was washed with an aqueous solution saturated with sodium bicarbonate, dried, treated with active charcoal and concentrated in vacuo. The residue was crystallized from methanol to yield 6-(4-fluorophenyl)imidazo[1,2-b][1,2,4]triazine (1.55 g). The filtrate was concentrated in vacuo and the residue was purified by column chromatography on silica gel (eluted with 1% methanol in dichloromethane) to yield second crop (0.64 g).

mp : 183-184°C

IR (Nujol) : 3130, 1600, 1323, 1215, 1200, 1155, 1145, 840, 750 cm^{-1}

NMR ($CDCl_3$, δ) : 7.18 (2H, t, J=9Hz), 8.07 (2H, dd, J=5Hz, 9Hz), 8.22 (1H, s), 8.33 (1H, d, J=2Hz), 8.42 (1H, d, J=2Hz)

The following compounds were obtained according to a similar manner to that of Preparation 1-(1).

(2) 6-(Benzo[b]thiophen-3-yl)imidazo[1,2-b][1,2,4]-triazine

mp : 174-176°C

IR (Nujol) : 1560, 1420, 1290, 1225, 1120, 1030, 1000, 900, 870, 760, 740 cm^{-1}

NMR ($CDCl_3$, δ) : 7.37-7.58 (2H, m), 7.96 (1H, d, J=7Hz), 8.16 (1H, s), 8.36 (2H, s), 8.46 (1H, s), 8.56 (1H, d, J=7Hz)

(3) 6-(3-Fluorophenyl)imidazo[1,2-b][1,2,4]triazine

mp : 160-161°C

IR (Nujol) : 3130, 1595, 1485, 1470, 1320, 1230, 1220, 1140, 1030, 960, 875, 745 cm^{-1}

NMR ($CDCl_3$, δ) : 7.12 (1H, t, J=9Hz), 7.45 (1H, td, J=8Hz, 5Hz), 7.76-7.86 (2H, m), 8.28 (1H, s), 8.38 (1H, d, J=2Hz), 8.46 (1H, d, J=2Hz)

(4) 6-(4-Chlorophenyl)imidazo[1,2-b][1,2,4]triazine

mp : 191-192°C

IR (Nujol) : 3090, 1220, 1155, 1085, 835, 775, 750 cm^{-1}

NMR ($CDCl_3$, δ) : 7.45 (2H, d, J=8Hz), 8.01 (2H, d, J=8Hz), 8.25 (1H, s), 8.35 (1H, d, J=2Hz), 8.45 (1H, d, J=2Hz)

(5) 6-(5-Chlorothiophen-2-yl)imidazo[1,2-b][1,2,4]-triazine

mp : 193-194°C

IR (Nujol) : 3100, 1140, 1025 cm^{-1}

NMR ($CDCl_3$, δ) : 6.95 (1H, d, J=4Hz), 7.40 (1H, d, J=4Hz), 8.10 (1H, s), 8.32 (1H, d, J=2Hz), 8.42 (1H, d, J=2Hz)

(6) 6-(5-Methylthiophen-2-yl)imidazo[1,2-b][1,2,4]-triazine

mp : 176-177.5°C

IR (Nujol) : 1570, 1520, 1360, 1230, 1210, 1145, 1025, 805 cm^{-1}

NMR ($CDCl_3$, δ) : 2.57 (3H, s), 6.79 (1H, d, J=4Hz), 7.48 (1H, d, J=4Hz), 8.10 (1H, s), 8.30 (1H, d, J=2Hz), 8.38 (1H, d, J=2Hz)

(7) 6-(4'-Fluorobiphenyl-4-yl)imidazo[1,2-b][1,2,4]-triazine

mp : 258-260°C

IR (Nujol) : 1520, 1480, 1320, 1240, 1220, 1200, 1155, 1030, 830, 750 cm^{-1}

NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 7.15 (2H, t, J=9Hz), 7.63 (2H, dd, J=6Hz, 9Hz), 7.70 (2H, d, J=9Hz), 8.11 (2H, d, J=9Hz), 8.37 (1H, s), 8.42 (1H, d, J=2Hz), 8.48 (1H, d, J=2Hz)

(8) 6-(3-Trifluoromethylphenyl)imidazo[1,2-b][1,2,4]-triazine

mp : 171-172.5°C

IR (Nujol) : 3125, 1440, 1340, 1310, 1220, 1160, 1115, 1095, 1070 cm^{-1}

NMR ($CDCl_3$, δ) : 7.57-7.71 (2H, m), 8.26 (1H, d, J=8Hz), 8.31-8.37 (2H, m), 8.38 (1H, d, J=2Hz), 8.48 (1H, d, J=2Hz)

(9) 6-(4-Ethoxycarbonylphenyl)imidazo[1,2-b][1,2,4]-triazine

mp : 193.5-195°C
IR (Nujol) : 1690, 1610, 1485, 1310, 1280, 1220, 1160, 1025 cm^{-1}
NMR ($CDCl_3$, δ) : 1.44 (3H, t, J=7Hz), 4.42 (2H, q, J=7Hz), 8.16 (4H, s), 8.36 (1H, s), 8.38 (1H, d, J=2Hz), 8.48 (1H, d, J=2Hz)

(10) 6-(4-(Fluoro-1-naphthyl)imidazo[1,2-b][1,2,4]triazine
mp : 170.5-172°C
IR (Nujol) : 1600, 1520, 1350, 1320, 1260, 1240, 1220, 1090, 1030, 830, 760 cm^{-1}
NMR ($CDCl_3$, δ) : 7.27 (1H, t, J=9Hz), 7.56-7.70 (2H, m), 7.88 (1H, dd, J=5Hz, 9Hz), 8.23 (1H, m), 8.28 (1H, s), 8.42 (1H, d, J=2Hz), 8.50 (1H, d, J=2Hz), 8.77 (1H, m)

(11) 6-(5-Bromothiophen-2-yl)imidazo[1,2-b][1,2,4]triazine
mp : 199.5-200.5°C
IR (Nujol) : 1560, 1520, 1495, 1465, 1360, 1280, 1220, 1200, 1145, 1025, 805 cm^{-1}
NMR ($CDCl_3$, δ) : 7.10 (1H, d, J=5Hz), 7.38 (1H, d, J=5Hz), 8.12 (1H, s), 8.34 (1H, d, J=2Hz), 8.45 (1H, d, J=2Hz)

(12) 6-(3-Methylbenzo[b]thiophen-2-yl)imidazo[1,2-b]-[1,2,4]triazine
mp : 252.5-253.5°C
IR (Nujol) : 1565, 1520, 1305, 1225, 1150, 1140, 1030, 730 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 8:1, δ) : 2.75 (3H, s), 7.38-7.48 (2H, m), 7.82 (1H, m), 7.88 (1H, m), 8.30 (1H, s), 8.40 (1H, d, J=2Hz), 8.48 (1H, d, J=2Hz)

Preparation 2

(1) A mixture of 6-(4-fluorophenyl)imidazo[1,2-b][1,2,4]-

triazine (2.19 g) and sodium borohydride (584 mg) in absolute ethanol (25 ml) was heated under reflux for 2 hours. After cooling, the reaction mixture was poured into ice-cold water. The separated solid was collected, washed with water and dried to yield 6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (1.917 g).

mp : 213-218°C (dec.)

IR (Nujol) : 3250, 3160, 1620, 1495, 1210, 835, 735 cm^{-1}

NMR (CD_3OD, δ) : 3.28 (2H, t, J=6Hz), 3.43 (2H, t, J=6Hz), 6.83 (1H, s), 7.02 (2H, t, J=9Hz), 7.55 (2H, dd, J=5Hz, 9Hz)

The following compounds were obtained according to a similar manner to that of Preparation 2-(1).

(2) 6-(Benzo[b]thiophen-3-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine

mp : 180-182°C

IR (Nujol) : 3250, 3220, 1635, 1420, 1375, 1060, 1015, 830, 760, 740 cm^{-1}

NMR (DMSO-d_6, δ) : 3.12 (2H, br), 3.27 (2H, br), 6.28 (1H, t, J=7Hz), 6.63 (1H, s, br), 7.15 (1H, s), 7.32-7.47 (2H, m), 7.67 (1H, s), 7.97 (1H, d, J=6Hz), 8.37 (1H, d, J=6Hz)

(3) 6-(3-Fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b]-[1,2,4]triazine

mp : 200-201°C

IR (Nujol) : 3180, 1620, 1580, 1335, 1305, 1200, 1075, 965, 860, 740 cm^{-1}

NMR ($CDCl_3$: CD_3OD = 10:1, δ) : 3.29 (2H, t, J=6Hz), 3.45 (2H, t, J=6Hz), 6.88 (1H, s), 6.83-6.95 (1H, m), 7.24-7.41 (3H, m)

(4) 6-(4-Chlorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b]-[1,2,4]triazine
mp : >250°C
IR (Nujol) : 3160, 1605, 1480, 1082, 842 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 3.27 (2H, t, J=6Hz), 3.43 (2H, t, J=6Hz), 6.88 (1H, s), 7.29 (2H, d, J=8Hz), 7.50 (2H, d, J=8Hz)

(5) 6-(5-Chlorothiophen-2-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine
mp : 215-220°C (dec.)
IR (Nujol) : 3200, 3100, 1623, 1035, 790 cm^{-1}
NMR ($CDCl_3$: CD_3OD = 9:1, δ) : 3.30 (2H, t, J=5Hz), 3.42 (2H, t, J=5Hz), 6.71 (1H, s), 6.80 (1H, d, J=4Hz), 6.90 (1H, d, J=4Hz)

(6) 6-(5-Methylthiophen-2-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine
mp : 183.5-185.5°C (dec.)
IR (Nujol) : 3250, 3200, 3150, 1630, 1380, 1060, 810, 715 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 2.46 (3H, s), 3.28 (2H, t, J=7Hz), 3.34-3.47 (2H, m), 6.63 (1H, d, J=4Hz), 6.68 (1H, s), 6.93 (1H, d, J=4Hz)

(7) 6-(4'-Fluorobiphenyl-4-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine
mp : 253-255°C
IR (Nujol) : 3200, 1670, 1620, 1510, 1490, 1335, 1235, 1160, 820 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 3.33 (2H, t, J=5Hz), 3.46 (2H, t, J=5Hz), 6.90 (1H, s), 7.13 (2H, t, J=9Hz), 7.50-7.69 (6H, m)

(8) 6-(3-Trifluoromethylphenyl)-1,2,3,4-

tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 210-211°C
IR (Nujol) : 3240, 3200, 3150, 1635, 1455, 1320, 1295, 1150, 1110, 1100 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 8:1, δ) : 3.31 (2H, t, J=6Hz), 3.44 (2H, t, J=6Hz), 6.94 (1H, s), 7.39-7.52 (2H, m), 7.76 (1H, m), 7.83 (1H, s)

(9) 6-(4-(Ethoxycarbonylphenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 283-286°C
IR (Nujol) : 3610, 3220, 1690, 1620, 1610, 1310, 1270, 1175, 1115 cm^{-1}
NMR (DMSO-d_6, δ) : 1.33 (3H, t, J=7Hz), 3.03-3.17 (2H, m), 3.18-3.30 (2H, m), 4.29 (2H, q, J=7Hz), 6.33 (1H, t, J=7Hz), 6.69 (1H, br s), 7.30 (1H, s), 7.74 (2H, d, J=9Hz), 7.85 (2H, d, J=9Hz)

(10) 6-(4-Fluoro-1-naphthyl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine
mp : 195-196.5°C
IR (Nujol) : 3250, 3180, 1615, 1590, 1335, 1260, 1230, 1145, 830, 760, 660 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 3.35-3.45 (2H, m), 3.45-3.55 (2H, m), 6.78 (1H, s), 7.15 (1H, dd, J=9Hz, 10Hz), 7.48-7.62 (3H, m), 8.14 (1H, m), 8.43 (1H, m)

(11) 6-(5-Bromothiophen-2-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine
mp : >360°C
IR (Nujol) : 3200, 3090, 1620, 1355, 1025, 960, 790 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 8:1, δ) : 3.29 (2H, t, J=6Hz), 3.45-3.57 (2H, m), 6.72 (1H, s), 6.88 (1H, d,

J=5Hz), 6.94 (1H, d, J=5Hz)

(12) 6-(3-Methylbenzo[b]thiophen-2-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 215.5-217.0°C
IR (Nujol) : 3250, 1620, 1360, 1280, 920, 750 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 2.46 (3H, s), 3.31-3.50 (4H, m), 6.72 (1H, s), 7.25-7.40 (2H, m), 7.68 (1H, d, J=8Hz), 7.80 (1H, d, J=8Hz)

Preparation 3

(1) A mixture of 6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (436 mg), triethylamine (0.9 ml) and acetic anhydride (0.5 ml) in 1,2-dichloroethane (10 ml) was heated under reflux for 3 hours. After cooling, the reaction mixture was concentrated in vacuo and the residue was dissolved in dichloromethane. The solution was washed with an aqueous solution saturated with sodium bicarbonate, dried and concentrated in vacuo. The residue was crystallized from diethyl ether to yield 1,4-diacetyl-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (562 mg).
mp : 145-147°C
IR (Nujol) : 3100, 1700, 1675, 1325, 1230, 840 cm^{-1}
NMR ($CDCl_3$, δ) : 2.25 (3H, s), 2.78 (3H, s), 3.90-4.05 (4H, m), 7.08 (2H, t, J=9Hz), 7.23 (1H, s), 7.72 (2H, dd, J=5Hz, 9Hz)

The following compounds were obtained according to a similar manner to that of Preparation 3-(1).

(2) 6-(Benzo[b]thiophen-3-yl)-1,4-diacetyl-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 120-126°C
IR (Nujol) : 1670, 1550, 1420, 1330, 1300, 1230,

1010, 830, 760 cm^{-1}

NMR ($CDCl_3$, δ) : 2.29 (3H, s), 2.81 (3H, s), 3.92-4.12 (4H, m), 7.33-7.51 (3H, m), 7.77 (1H, s), 7.92 (1H, d, J=7Hz), 8.25 (1H, d, J=7Hz)

(3) 1,4-Diacetyl-6-(3-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 169.5-171°C

IR (Nujol) : 3100, 1705, 1675, 1610, 1585, 1560, 1540, 1480, 1330, 1235, 1215, 855 cm^{-1}

NMR ($CDCl_3$, δ) : 2.55 (3H, s), 2.78 (3H, s), 3.90-4.08 (4H, m), 6.98 (1H, dt, J=2Hz, 9Hz), 7.38-7.55 (4H, m)

(4) 6-(4-Chlorophenyl)-1,4-diacetyl-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 172-174°C

IR (Nujol) : 1690, 1640, 1535, 1350, 1335, 1300, 1205, 1150, 1010, 840, 740 cm^{-1}

NMR ($CDCl_3$, δ) : 2.25 (3H, s), 2.78 (3H, s), 3.80-4.08 (4H, m), 7.28 (1H, s), 7.37 (2H, d, J=8Hz), 7.69 (2H, d, J=8Hz)

(5) 6-(5-Chlorothiophen-2-yl)-1,4-diacetyl-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 153-154°C

IR (Nujol) : 3130, 1703, 1675, 1550, 1320, 1290, 1230 cm^{-1}

NMR ($CDCl_3$, δ) : 2.24 (3H, s), 2.72 (3H, s), 3.85-4.05 (4H, m), 6.84 (1H, d, J=4Hz), 7.02 (1H, d, J=4Hz), 7.13 (1H, s)

(6) 1,4-Diacetyl-6-(5-methylthiophen-2-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 153-154.5°C

IR (Nujol) : 3105, 1700, 1680, 1550, 1470, 1330, 1300, 1260, 1240, 1220, 1080, 810 cm^{-1}

NMR ($CDCl_3$, δ) : 2.24 (3H, s), 2.50 (3H, s), 2.73 (3H, s), 3.87-4.03 (4H, m), 6.69 (1H, d, J=4Hz), 7.07 (1H, d, J=4Hz), 7.09 (1H, s)

(7) 1,4-Diacetyl-6-(4'-fluorobiphenyl-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 177-178°C

IR (Nujol) : 1710, 1670, 1560, 1545, 1490, 1335, 1220, 825 cm^{-1}

NMR ($CDCl_3$, δ) : 2.23 (3H, s), 2.80 (3H, s), 3.90-4.08 (4H, m), 7.14 (2H, t, J=9Hz), 7.34 (1H, s), 7.57 (2H, d, J=9Hz), 7.59 (2H, dd, J=5Hz, 9Hz), 7.82 (2H, d, J=9Hz)

(8) 1,4-Diacetyl-6-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 115-121°C (an amorphous powder)

IR (Nujol) : 1680, 1570, 1550, 1330, 1300, 1260, 1160, 1120, 800, 700 cm^{-1}

NMR ($CDCl_3$, δ) : 2.27 (3H, s), 2.78 (3H, s), 3.91-4.08 (4H, m), 7.37 (1H, s), 7.51-7.58 (2H, m), 7.94 (1H, m), 7.99 (1H, s)

(9) 1,4-Diacetyl-6-(4-ethoxycarbonylphenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 159-161°C

IR (Nujol) : 1705, 1680, 1610, 1570, 1550, 1335, 1280, 1260, 1120, 1100, 1015 cm^{-1}

NMR ($CDCl_3$, δ) : 1.40 (3H, t, J=7Hz), 2.27 (3H, s), 2.80 (3H, s), 3.92-4.08 (4H, m), 4.39 (2H, q, J=7Hz), 7.40 (1H, s), 7.81 (2H, d, J=9Hz), 8.07 (2H, d, J=9Hz)

(10) 1,4-Diacetyl-6-(4-fluoro-1-naphthyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 133-135°C
IR (Nujol) : 1690, 1670, 1555, 1540, 1350, 1335, 1220, 1210, 1140, 770 cm^{-1}
NMR ($CDCl_3$, δ) : 2.30 (3H, s), 2.79 (3H, s), 3.96-4.14 (4H, m), 7.19 (1H, dd, J=9Hz, 10Hz), 7.28 (1H, s), 7.56-7.62 (2H, m), 7.67 (1H, dd, J=5Hz, 9Hz), 8.17 (1H, m), 8.55 (1H, m)

(11) 1,4-Diacetyl-6-(5-bromothiophen-2-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 154-155.5°C
IR (Nujol) : 3120, 1705, 1675, 1550, 1320, 1295, 1230, 1000, 805, 745 cm^{-1}
NMR ($CDCl_3$, δ) : 2.25 (3H, s), 2.73 (3H, s), 3.88-4.07 (4H, m), 6.98 (1H, d, J=3Hz), 7.02 (1H, d, J=3Hz), 7.15 (1H, s)

(12) 1,4-Diacetyl-6-(3-methylbenzo[b]thiophen-2-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 171.5-173°C
IR (Nujol) : 1690, 1680, 1540, 1360, 1340, 1300, 1210, 755 cm^{-1}
NMR ($CDCl_3$, δ) : 2.30 (3H, s), 2.60 (3H, s), 2.80 (3H, s), 3.90-4.10 (4H, m), 7.21-7.44 (3H, m), 7.72 (1H, d, J=8Hz), 7.82 (1H, d, J=8Hz)

Preparation 4

To a solution of 2-pyridinecarbaldehyde (10 g) in a mixture of methanol (10 ml) and 10% aqueous sodium hydroxide solution (20 ml) was added dropwise 4'-fluoroacetophenone (8.288 g) over a period of 1 hour at 0-10°C. After the mixture was stirred for 1 hour at 0-10°C, the separated solid was collected, washed with

water and dried. The solid was recrystallized from ethanol to yield (Z)-1-(4-fluorophenyl)-3-(pyridin-2-yl)-2-propen-1-one (9.21 g).

mp : 207.5-209.5°C

IR (Nujol) : 1665, 1615, 1600, 1585, 1510, 1435, 1325, 1215, 1160, 1020, 975, 865, 780 cm^{-1}

NMR ($CDCl_3$, δ) : 7.18 (2H, t, J=9Hz), 7.33 (1H, ddd, J=7Hz, 5Hz, 2Hz), 7.49 (1H, d, J=7Hz), 7.76 (1H, td, J=7Hz, 2Hz), 7.78 (1H, d, J=15Hz), 8.12 (1H, d, J=15Hz), 8.15 (2H, dd, J=5Hz, 9Hz), 8.71 (1H, d, J=5Hz)

Preparation 5

A solution of (Z)-1-(4-fluorophenyl)-3-(pyridin-2-yl)-2-propen-1-one (6.512 g) in ethanol (86 ml) was hydrogenated over 5% palladium-on-charcoal catalyst (580 mg) at 4 atmospheric pressure of hydrogen for 5 hours at ambient temperature. The solution was filtered and the filtrate was concentrated in vacuo, and the residue was dissolved in ethanol (28 ml). To the solution was added dropwise 3.2N ethanolic hydrogen chloride (14.3 ml) at ambient temperature. The mixture was stirred for 20 minutes and the solvent was evaporated in vacuo. The residue was crystallized from a mixture of ethanol and diethyl ether to yield 1-(4-fluorophenyl)-3-(pyridin-2-yl)propan-1-one hydrochloride (4.5422 g).

mp : 166-168°C

IR (Nujol) : 2350, 2060, 1685, 1600, 1505, 1230, 1210, 1155, 980, 845, 780 cm^{-1}

NMR (DMSO-d_6, δ) : 3.40 (2H, t, J=7Hz), 3.77 (2H, t, J=7Hz), 7.39 (2H, t, J=9Hz), 7.89 (1H, t, J=8Hz), 8.02-8.15 (3H, m), 8.50 (1H, td, J=8Hz, 2Hz), 8.80 (1H, d, J=6Hz)

Preparation 6

To a solution of 1-(4-fluorophenyl)-3-(pyridin-2-yl)-propan-1-one hydrochloride (2.657 g) in hydrobromic acid (47% in water, 26.5 ml) was added dropwise bromine (0.526 ml) over a period of 20 minutes at 50°C. The mixture was stirred for 100 minutes at 50°C and cooled. The aqueous solution saturated with sodium bicarbonate was added to the mixture to adjust to pH 8 at 0°C. The aqueous solution was extracted twice with ethyl acetate. The combined organic layers were washed with sodium bicarbonate solution and brine successively, and dried over anhydrous sodium sulfate. The solution was concentrated to 30 ml of the volume and to the solution was added ethanol (100 ml). After evaporation of the solvent to 20 ml of the volume, to the solution was added 3-amino-1,2,4-triazine (1.922 g) in one portion. The mixture was heated under reflux for 1 hour with stirring and then the mixture was evaporated to dryness in vacuo. The residue was partitioned between 10% methanol in dichloromethane and 0.5N hydrochloric acid. The aqueous layer was extracted twice with dichloromethane and the combined organic layers were washed with water, the aqueous solution saturated with sodium bicarbonate and brine successively. The solution was dried over anhydrous sodium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane:methanol = 100:1 - 100:2 as the eluent) to yield 6-(4-fluorophenyl)-7-(2-pyridylmethyl)imidazo[1,2-b][1,2,4]triazine (35.3 mg).

NMR ($CDCl_3$, δ) : 4.87 (2H, s), 7.10-7.25 (3H, m), 7.30 (1H, t, J=8Hz), 7.70 (1H, td, J=8Hz, 2Hz), 8.05 (2H, dd, J=5Hz, 9Hz), 8.37 (1H, d, J=2Hz), 8.47 (1H, d, J=2Hz), 8.60 (1H, d, J=5Hz)

Preparation 7

To a suspension of sodium hydride (2.0 g) in anhydrous N,N-dimethylformamide (10 ml) was added dropwise a solution of 4-mercaptopyridine (5.55 g) in anhydrous N,N-dimethylformamide (30 ml) at 4°C under nitrogen atmosphere. The reaction mixture was stirred for 15 minutes at ambient temperature and cooled again. To the mixture was added dropwise a solution of 2-chloro-4'-fluoroacetophenone (8.63 g) in N,N-dimethylformamide (15 ml). The reaction mixture was stirred at ambient temperature overnight and poured into ice-water. The separated solid was collected, washed with water and dried to yield 1-(4-fluorophenyl)-2-(4-pyridylthio)ethan-1-one (5.7 g).

mp : 103-104°C

IR (Nujol) : 1675, 1590, 1580, 1195 cm^{-1}

NMR ($CDCl_3$, δ) : 4.39 (2H, s), 7.10-7.25 (4H, m), 8.02 (2H, dd, J=5Hz, 9Hz), 8.41 (2H, d, J=5Hz)

Preparation 8

To a solution of 1,2-dimethylimidazole (1.92 g) and triethylamine (2.02 g) in dichloromethane (20 ml) was added dropwise 4-fluorobenzoyl chloride (237 ml) at 4°C. The reaction mixture was stirred overnight at ambient temperature and then poured into water. The organic layer was separated, washed with aqueous solution saturated with sodium bicarbonate and brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel to yield 1-(4-fluorophenyl)-2-(1-methylimidazol-2-yl)ethan-1-one (1.7 g).

NMR ($CDCl_3$, δ) : 3.64 (3H, s), 6.89 (1H, s), 7.00 (1H, s), 7.15 (2H, t, J=9Hz), 8.16 (2H, dd, J=5Hz, 9Hz)

Preparation 9

(1) To a solution of 1-(4-fluorophenyl)-2-(4-pyridylthio)ethan-1-one (2.97 g) in anhydrous ethanol was added dropwise bromine (0.62 ml) at 4°C under nitrogen atmosphere. The mixture was stirred at ambient temperature for one hour and to the mixture was added 3-amino-1,2,4-triazine (2.3 g). The mixture was heated under reflux for 5 hours. After cooling, the mixture was concentrated in vacuo and to the residue was added an aqueous solution saturated with sodium bicarbonate. The separated oil was extracted with dichloromethane and the extract was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from ethanol to yield 6-(4-fluorophenyl)-7-(4-pyridylthio)-imidazo[1,2-b][1,2,4]triazine (820 mg).

mp : 189-190°C

IR (Nujol) : 1600, 1590, 1565, 1540, 1520, 1400, 1300, 1215, 1165, 1150, 1020, 840 cm^{-1}

NMR ($CDCl_3$, δ) : 6.91 (2H, d, J=5Hz), 7.18 (2H, t, J=9Hz), 8.32 (2H, dd, J=5Hz, 9Hz), 8.39 (2H, m), 8.47 (1H, d, J=3Hz), 8.61 (1H, d, J=3Hz)

The following compound was obtained according to a similar manner to that of Preparation 9-(1).

(2) 6-(4-Fluorophenyl)-7-(1-methylimidazol-2-yl)imidazo-[1,2-b][1,2,4]triazine

mp : 232-233°C

IR (Nujol) : 3140, 3100, 1605, 1540, 1520 cm^{-1}

NMR ($CDCl_3$, δ) : 3.49 (3H, s), 7.09 (2H, t, J=9Hz), 7.20 (1H, s), 7.44 (1H, s), 7.78 (2H, dd, J=5Hz, 9Hz), 8.42 (1H, d, J=2Hz), 8.55 (1H, d, J=2Hz)

Preparation 10

To a solution of 6-(4-fluorophenyl)-7-(4-pyridylthio)imidazo[1,2-b][1,2,4]triazine (323 mg) in dichloromethane was added 3-chloroperbenzoic acid (80%, 238 mg) at 4°C. The reaction mixture was stirred for 3 hours at ambient temperature. The solution was washed with an aqueous solution saturated with sodium bicarbonate, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from ethanol to yield 6-(4-fluorophenyl)-7-(4-pyridylsulfinyl)imidazo[1,2-b]-[1,2,4]triazine (180 mg)

mp : 244-245°C

IR (Nujol) : 3100, 3060, 1595, 1570, 1530, 1240, 1230, 1220, 1175, 1020, 840 cm^{-1}

NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 6.96 (2H, d, J=7Hz), 7.20 (2H, t, J=9Hz), 8.05 (2H, d, J=7Hz), 8.31 (2H, dd, J=5Hz, 9Hz), 8.49 (1H, d, J=2Hz), 8.63 (1H, d, J=2Hz)

Preparation 11

To a solution of 4'-fluoroacetophenone (585 g) in dichloromethane (2.93 ℓ) was added dropwise a solution of bromine (189.5 ml) in dichloromethane (70 ml) over a period of 2 hours. The mixture was stirred at ambient temperature for 1 hour and to the mixture was added water (1.4 ℓ). The organic layer was separated and washed with water (1.4 ℓ), an aqueous saturated sodium bicarbonate solution (1.4 ℓ) and brine (1.4 ℓ). The solution was dried and concentrated in vacuo. To the residue was added n-hexane (500 ml) and the solution was concentrated in vacuo. The obtained oil was crystallized from n-hexane (50 ml) and recrystallization from n-hexane (650 ml) gave 2-bromo-4'-fluoroacetophenone (499 g).

Example 1

(1) To a solution of 1,4-diacetyl-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (544 mg) in pyridine (1.5 ml) and dichloromethane (1.0 ml) was added dropwise ethyl chloroformate (0.9 ml) at 15°C. After stirring for 3 hours at ambient temperature, to the mixture was added pyridine (1.5 ml) in one portion and dropwise ethyl chloroformate (0.9 ml) at 15°C. The addition of pyridine (1.5 ml) and ethyl chloroformate (0.9 ml) was repeated three times. The mixture was stirred overnight at ambient temperature and then concentrated in vacuo and to the residue was added an aqueous solution saturated with sodium bicarbonate. The separated solid was collected, washed with water and dried to yield 1,4-diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b]-[1,2,4]-triazine (730 mg).

mp : 127-130°C

IR (Nujol) : 1705, 1670, 1550, 1335, 965, 840 cm^{-1}

The following compounds were obtained according to a similar manner to that of Example 1-(1).

(2) 6-(Benzo[b]thiophen-3-yl)-1,4-diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 167-170°C

IR (Nujol) : 1720, 1690, 1665, 1550, 1410, 1335, 1300, 1205, 1130, 980, 760 cm^{-1}

(3) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(3-fluorophenyl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine

mp : 157.5-158.5°C

IR (Nujol) : 1710, 1670, 1550, 1410, 1330, 1310,

1200, 1120, 975 cm^{-1}

(4) 6-(4-Chlorophenyl)-1,4-diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 172-177°C
IR (Nujol) : 1715, 1685, 1665, 1550, 1410, 1330, 1305, 1200, 1115, 835 cm^{-1}

(5) 6-(5-Chlorothiophen-2-yl)-1,4-diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 170-171°C
IR (Nujol) : 1703, 1675, 1558, 1410, 1330, 1305, 1200, 1115, 980, 950, 835, 795 cm^{-1}

(6) 7-(3-Chloro-1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-1,4-diacetyl-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 179-181°C
IR (Nujol) : 1720, 1685, 1660, 1555, 1500, 1340, 1300, 1210, 1120, 1000, 850 cm^{-1}

(7) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylquinolin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine
mp : 131-134°C (broad)
IR (Nujol) : 1705, 1680, 1550, 1500, 1490, 1310, 1300, 1285, 1225, 1040 cm^{-1}

(8) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(5-methylthiophen-2-yl)-1,2,3,4-tetrahydro-imidazo[1,2-b][1,2,4]triazine
mp : 185-185.5°C
IR (Nujol) : 1720, 1695, 1670, 1560, 1410, 1340,

1310, 1210, 1120 cm^{-1}

(9) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(4'-fluorobiphenyl-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 180-182°C
IR (Nujol) : 1710, 1660, 1560, 1410, 1335, 1305, 820 cm^{-1}

(10) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 203-204°C
IR (Nujol) : 1710, 1680, 1555, 1415, 1340, 1320, 1160, 1120, 970 cm^{-1}

(11) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(4-ethoxycarbonylphenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 147-150°C
IR (Nujol) : 1710, 1690, 1675, 1610, 1550, 1335, 1290, 1275, 1115 cm^{-1}

(12) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(4-fluoro-1-naphthyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 156-159°C (broad)
IR (Nujol) : 1710, 1675, 1540, 1335, 1310, 1200, 980, 760 cm^{-1}

(13) 6-(5-Bromothiophen-2-yl)-1,4-diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 182-183.5°C
IR (Nujol) : 1700, 1675, 1560, 1410, 1330, 1310,

1200, 1125, 980, 950, 795 cm^{-1}

(14) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(3-methylbenzo[b]thiophen-2-yl]-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 145-153°C (an amorphous powder)
IR (Nujol) : 1720, 1690, 1560, 1415, 1335, 1310, 1205, 1120, 980 cm^{-1}

(15) 1,4-Diacetyl-7-(1,4-dihydro-1-ethoxycarbonyl-3-methoxycarbonylpyridin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 178-179.5°C
IR (Nujol) : 1725, 1710, 1660, 1650, 1500, 1350, 1230, 1080, 1015, 840 cm^{-1}

Example 2

(1) To a suspension of 1,4-diacetyl-7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (690 mg) and decalin (5 ml) was added sulfur (64 mg) at 80°C. The temperature was raised to 170°C and the mixture was stirred for 2 hours. After cooling, the reaction mixture was purified by column chromatography on silica gel (eluted with 2% methanol in dichloromethane) and the obtained oil was crystallized from methanol to yield 1,4-diacetyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (500 mg).

mp : 212-214°C
IR (Nujol) : 1708, 1673, 1560, 1335, 1280, 1230, 1160, 845 cm^{-1}
NMR ($CDCl_3$, δ) : 1.83 (3H, s), 2.78 (3H, s), 3.42 (1H, m), 3.89 (1H, m), 4.07 (1H, m), 4.90 (1H, m), 7.01 (2H, t, J=9Hz), 7.30 (2H, d, J=5Hz), 7.48 (2H, dd, J=6Hz, 9Hz), 8.67 (2H, d, J=5Hz)

The following compounds were obtained according to a similar manner to that of Example 2-(1).

(2) 6-(Benzo[b]thiophen-3-yl)-1,4-diacetyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 262-263.5°C
IR (Nujol) : 1690, 1680, 1600, 1550, 1335, 1300, 1275, 835, 760, 710 cm^{-1}
NMR ($CDCl_3$, δ) : 1.93 (3H, br), 2.61 (3H, s), 3.56 (1H, br), 3.90 (1H, br), 4.13 (1H, br), 4.93 (1H, br), 7.33 (2H, d, J=6Hz), 7.32-7.46 (3H, m), 7.85-7.94 (2H, m), 8.54 (2H, d, J=6Hz)

(3) 1,4-Diacetyl-6-(3-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 190-191.5°C
IR (Nujol) : 1690, 1675, 1595, 1560, 1335, 1295, 1190, 1010, 880, 870, 830 cm^{-1}

(4) 6-(4-Chlorophenyl)-1,4-diacetyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 200-202°C
IR (Nujol) : 1702, 1680, 1600, 1550, 1325, 1280, 1245 cm^{-1}

(5) 6-(5-Chlorothiophen-2-yl)-1,4-diacetyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 206-207°C
IR (Nujol) : 1700, 1665, 1555, 1330, 995, 800, 715 cm^{-1}

(6) 7-(3-Chloropyridin-4-yl)-1,4-diacetyl-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b]-[1,2,4]triazine
mp : 209-210°C

IR (Nujol) : 1695, 1670, 1553, 1335, 1300, 1220, 845 cm^{-1}

(7) 1,4-Diacetyl-6-(4-fluorophenyl)-7-(4-quinolyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 148-151°C (broad)
IR (Nujol) : 1700, 1670, 1550, 1315, 1220, 1150, 830 cm^{-1}

(8) 1,4-Diacetyl-6-(5-methylthiophen-2-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 198-199°C
IR (Nujol) : 1710, 1680, 1600, 1560, 1320, 1290, 800 cm^{-1}

(9) 1,4-Diacetyl-6-(4'-fluorobiphenyl-4-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 186-188°C
IR (Nujol) : 1690, 1675, 1600, 1550, 1340, 1300, 830 cm^{-1}

(10) 1,4-Diacetyl-7-(pyridin-4-yl)-6-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]-triazine
mp : 211-212°C
IR (Nujol) : 1690, 1680, 1600, 1560, 1335, 1290, 1280, 1165, 1115, 700 cm^{-1}

(11) 1,4-Diacetyl-6-(4-ethoxycarbonylphenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 169-172°C
IR (Nujol) : 1710, 1680, 1605, 1565, 1555, 1275, 1250, 1190, 1105 cm^{-1}

(12) 1,4-Diacetyl-6-(4-fluoro-1-naphthyl)-7-(pyridin-4-

yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 168-170°C
IR (Nujol) : 1690, 1680, 1600, 1550, 1465, 1375, 1340, 1300, 760 cm^{-1}

(13) 6-(5-Bromothiophen-2-yl)-1,4-diacetyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 192-193.5°C
IR (Nujol) : 1700, 1670, 1550, 1350, 1330, 1200, 990, 965, 940, 710 cm^{-1}

(14) 1,4-Diacetyl-6-(3-methylbenzo[b]thiophen-2-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b]-[1,2,4]triazine
mp : 170-173°C
IR (Nujol) : 1690, 1600, 1555, 1525, 1285, 1245, 1190 cm^{-1}

(15) 1,4-Diacetyl-6-(4-fluorophenyl)-7-(3-methoxycarbonyl-pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b]-[1,2,4]triazine
mp : 178-179.5°C
IR (Nujol) : 1720, 1705, 1690, 1555, 1330, 1300, 1120, 835 cm^{-1}

Example 3

(1) To 1,4-diacetyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (379 mg) was added 4% methanolic sodium hydroxide (5 ml). After stirring for 3 hours at ambient temperature, the mixture was poured into ice-cold water. The solid was collected, washed with water and dried. The solid was recrystallized from ethanol to yield 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (237 mg).
mp : 214-216°C

IR (Nujol) : 3300-2600 (br), 1625, 1595, 1330, 1242, 1215, 1080, 980, 835, 815, 730, 695 cm^{-1}

NMR (DMSO-d_6, δ) : 3.04 (2H, br), 3.29 (2H, br), 6.31 (1H, t, J=6Hz), 6.99 (1H, br), 7.10 (2H, t, J=9Hz), 7.30 (2H, d, J=6Hz), 7.40 (2H, dd, J=5Hz, 9Hz), 8.46 (2H, d, J=6Hz)

The following compounds were obtained according to a similar manner to that of Example 3-(1).

(2) 6-(Benzo[b]thiophen-3-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimiazo[1,2-b][1,2,4]triazine

mp : 211-213°C

IR (Nujol) : 3620, 3180, 3070, 1620, 1590, 1245, 1000, 990, 820, 760, 740 cm^{-1}

NMR ($CDCl_3$, δ) : 3.20-3.40 (4H, m), 4.57 (1H, t, J=7Hz), 7.26 (2H, dd, J=1Hz, 6Hz), 7.26-7.43 (4H, m), 7.78 (1H, d, J=7Hz), 7.87 (1H, d, J=7Hz), 8.37 (2H, dd, J=1Hz, 6Hz)

(3) 6-(3-Fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 222-223°C

IR (Nujol) : 3240, 3150, 3070, 1630, 1590, 1420, 1330, 1270, 1200, 1160, 950, 870, 790 cm^{-1}

NMR (DMSO-d_6, δ) : 3.00-3.12 (2H, m), 3.24-3.35 (2H, m), 6.32 (1H, t, J=7Hz), 6.94-7.06 (2H, m), 7.12-7.30 (3H, m), 7.32 (2H, d, J=6Hz), 8.50 (2H, d, J=6Hz)

(4) 6-(4-Chlorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 214-215°C (dec.)

IR (Nujol) : 3220, 3170, 3130, 1620, 1595, 1325, 1240, 975, 830 cm^{-1}

NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 3.23 (2H, t, J=5Hz), 3.49 (2H, t, J=5Hz), 7.20-7.45 (6H, m), 8.40 (2H, d, J=6Hz)

(5) 6-(5-Chlorothiophen-2-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 220-223°C (dec.)
IR (Nujol) : 3225, 3170, 3080, 1620, 1592, 1330, 795 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 3.25 (2H, t, J=5Hz), 3.47 (2H, t, J=5Hz), 6.79 (1H, d, J=4Hz), 6.87 (1H, d, J=4Hz), 7.53 (2H, d, J=6Hz), 8.49 (2H, d, J=6Hz)

(6) 7-(3-Chloropyridin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 205-207°C
IR (Nujol) : 3660, 3220, 3160, 1610, 1595, 1215, 840 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 3.15 (2H, br), 3.44 (2H, t, J=5Hz), 6.91 (2H, t, J=9Hz), 7.23 (2H, dd, J=6Hz, 9Hz), 7.31 (1H, d, J=6Hz), 8.38 (1H, d, J=6Hz), 8.57 (1H, s)

(7) 6-(4-Fluorophenyl)-7-(4-quinolyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 216-218°C (dec.)
IR (Nujol) : 3200, 1590, 1510, 1500, 1330, 1320, 1215, 1150, 840 cm^{-1}
NMR ($CDCl_3$, δ) : 3.28 (2H, m), 3.52 (2H, m), 4.43 (1H, t, J=8Hz), 5.89 (1H, s), 6.78 (2H, t, J=9Hz), 7.27 (2H, m), 7.39 (1H, d, J=5Hz), 7.47 (1H, m), 7.70 (2H, m), 8.17 (1H, d, J=9Hz), 8.98 (1H, d, J=5Hz)

(8) 6-(5-Methylthiophen-2-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 212-213.5°C
IR (Nujol) : 3230, 3210, 1625, 1595, 1240, 1210, 830, 805 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 2.45 (3H, s), 3.27 (2H, t, J=5Hz), 3.48 (2H, t, J=5Hz), 6.58 (1H, d, J=4Hz), 6.87 (1H, d, J=4Hz), 7.47 (2H, dd, J=1Hz, 6Hz), 8.45 (2H, dd, J=1Hz, 6Hz)

(9) 6-(4'-Fluorobiphenyl-4-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 229.5-230.5°C
IR (Nujol) : 3220, 1640, 1600, 1510, 1340, 1220, 830 cm^{-1}
NMR (DMSO-d_6, δ) : 3.02-3.15 (2H, m), 3.27-3.38 (2H, m), 6.32 (1H, t, J=7Hz), 7.00 (1H, br m), 7.28 (2H, t, J=9Hz), 7.36 (2H, d, J=6Hz), 7.51 (2H, d, J=9Hz), 7.58 (2H, d, J=9Hz), 7.72 (2H, dd, J=5Hz, 9Hz), 8.48 (2H, d, J=6Hz)

(10) 7-(Pyridin-4-yl)-6-(3-trifluoromethylphenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 225.5-226.5°C
IR (Nujol) : 3180, 3100, 1620, 1600, 1305, 1180, 1170, 1130, 800 cm^{-1}
NMR ($CDCl_3$, δ) : 3.30-3.42 (2H, m), 3.52 (2H, t, J=5Hz), 4.64 (1H, m), 6.66 (1H, br), 7.30 (2H, dd, J=1Hz, 5Hz), 7.33 (1H, m), 7.42-7.52 (2H, m), 7.80 (1H, s), 8.55 (2H, dd, J=1Hz, 5Hz)

(11) 6-(5-Bromothiophen-2-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 232.5-233.5°C
IR (Nujol) : 3200, 3150, 3050, 1620, 1590, 1360, 1330, 1235, 940, 795 cm^{-1}

NMR (DMSO-d_6, δ) : 2.97-3.09 (2H, br), 3.22-3.32 (2H, br), 6.30 (1H, t, J=5Hz), 6.83 (1H, d, J=4Hz), 7.03 (1H, d, J=4Hz), 7.14 (1H, br s), 7.47 (2H, d, J=6Hz), 8.55 (2H, d, J=6Hz)

(12) 6-(3-Methylbenzo[b]thiophen-2-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 217.5-220°C

IR (Nujol) : 3200, 1590, 1535, 1365, 1240, 820, 755 cm^{-1}

NMR ($CDCl_3$, δ) : 1.89 (3H, s), 3.26-3.41 (2H, m), 3.47-3.60 (2H, m), 5.20 (1H, s), 7.24-7.46 (5H, m), 7.58 (1H, m), 7.78 (1H, m), 8.45 (2H, d, J=6Hz)

Example 4

(1) A mixture of 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (300 mg), triethylamine (156 µl) and acetic anhydride (106 µl) in 1,2-dichloroethane (3 ml) was refluxed for 1.5 hours under nitrogen. After cooling, the reaction mixture was concentrated in vacuo and the residue was partitioned between dichloromethane and an aqueous solution saturated with sodium bicarbonate. The aqueous layer was extracted with dichloromethane and the combined organic layers were washed with brine and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the crude product was purified by recrystallization from ethanol to give 4-acetyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (245 mg).

mp : 236-238°C

IR (Nujol) : 3230, 1670, 1605, 1545, 1515, 1380, 1220, 840 cm^{-1}

NMR (DMSO-d_6, δ) : 2.69 (3H, s), 3.28 (2H, m),

3.80 (2H, t, J=5Hz), 6.57 (1H, t, J=7Hz), 7.15 (2H, t, J=9Hz), 7.38 (2H, dd, J=1Hz, 6Hz), 7.48 (2H, dd, J=6Hz, 9Hz), 8.59 (2H, dd, J=1Hz, 6Hz)

The following compound was obtained according to a similar manner to that of Example 4-(1).

(2) 6-(4-Fluorophenyl)-4-pentafluoropropanoyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 186-187°C
IR (Nujol) : 1730, 1630, 1600, 1515, 1230, 1220, 1100, 1010, 940 cm^{-1}
FAB MASS : 442 $(M+H)^+$

Example 5

(1) To a mixture of 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (13 g) and 37% aqueous formaldehyde (38.7 ml) in methanol (520 ml) was added sodium cyanoborohydride (27.7 g) in several portions at ambient temperature. After the addition was completed, the reaction mixture was stirred for 10 minutes at the same temperature, and then acetic acid (46.4 ml) was added dropwise to neutralize the solution during a period of 1.5 hours. After stirring for half an hour, 37% aqueous formaldehyde (77.4 ml) was added in one portion and sodium cyanoborohydride (55.4 g) was added in several portions at room temperature during a period of 2 hours. The solution was always adjusted to pH 7 with acetic acid. After being stirred for additional 2 hours at the same temperature, the solvent was evaporated under reduced pressure and the residue was partitioned between dichloromethane and an aqueous solution saturated with sodium bicarbonate. The aqueous layer was extracted twice with dichloromethane. The combined organic layers were

washed with an aqueous solution saturated with sodium bicarbonate and brine successively, and dried over anhydrous sodium sulfate. The solution was concentrated in vacuo and the residue was purified by column chromatography on silica gel (dichloromethane:methanol = 100:1.5 - 100:5 as eluent) to give a solid which was recrystallized from ethyl acetate to provide 6-(4-fluorophenyl)-4-methyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (2.14 g).

mp : 181-182.5°C

IR (Nujol) : 3240, 1600, 1585, 1505, 1405, 1360, 1205, 835, 805 cm^{-1}

NMR ($CDCl_3$, δ) : 3.20 (3H, s), 3.32-3.50 (4H, m), 4.75 (1H, t, J=7Hz), 6.97 (2H, t, J=9Hz), 7.30 (2H, dd, J=1Hz, 6Hz), 7.46 (2H, dd, J=5Hz, 9Hz), 8.47 (2H, dd, J=1Hz, 6Hz)

The following compound was obtained according to a similar manner to that of Example 5-(1).

(2) 6-(4-Chlorophenyl)-4-methyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 158-160°C

IR (Nujol) : 3150, 1580, 1500, 1415, 1360, 1330, 1085, 990, 820 cm^{-1}

NMR ($CDCl_3$, δ) : 3.24 (3H, s), 3.33-3.50 (4H, m), 4.84 (1H, t, J=7Hz), 7.25 (2H, d, J=9Hz), 7.33 (2H, dd, J=1Hz, 6Hz), 7.44 (2H, d, J=9Hz), 8.48 (2H, dd, J=1Hz, 6Hz)

Example 6

(1) To a mixture of 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (118 mg) and triethylamine (0.09 ml) in dichloromethane (5 ml) was added benzoyl chloride (68 mg). After stirring for 5

hours at ambient temperature, the mixture was washed with an aqueous solution saturated with sodium bicarbonate, dried and concentrated in vacuo. The oily residue was purified by column chromatography on silica gel (eluted with 2% methanol in dichloromethane) and the obtained oil was crystallized from a mixture of ethyl acetate and diethyl ether to yield 4-benzoyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]-triazine (95 mg).

mp : 237-238°C

IR (Nujol) : 3200, 1650, 1510, 1350, 1240, 1215, 970, 840, 810, 780, 730, 700 cm^{-1}

NMR ($CDCl_3$, δ) : 3.50 (2H, t, J=6Hz), 4.07 (2H, t, J=6Hz), 6.83 (2H, t, J=9Hz), 7.09 (2H, dd, J=5Hz, 9Hz), 7.30-7.65 (7H, m), 8.54 (2H, d, J=6Hz)

The following compound was obtained according to a similar manner to that of Example 6-(1).

(2) 6-(4-Fluorophenyl)-4-methylsulfonyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 223-224.5°C

IR (Nujol) : 3245, 1535, 1340, 1208, 1155, 830 cm^{-1}

NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 3.43 (2H, t, J=5Hz), 3.60 (3H, s), 3.93 (2H, t, J=5Hz), 6.98 (2H, t, J=9Hz), 7.41 (2H, d, J=5Hz), 7.45 (2H, dd, J=5Hz, 9Hz), 8.52 (2H, d, J=5Hz)

(3) 4-{3-[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]-propenoyl}-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 235-238°C

IR (Nujol) : 3630, 1650, 1600, 1540, 1510 cm^{-1}

NMR ($CDCl_3$, δ) : 1.43 (18H, s), 3.49 (2H, q, J=6Hz),

4.10 (2H, t, J=6Hz), 4.80 (1H, t, J=6Hz), 5.52 (1H, s), 6.90 (2H, t, J=9Hz), 7.39 (2H, d, J=6Hz), 7.48 (2H, s), 7.51 (2H, dd, J=5Hz, 9Hz), 7.85 (1H, d, J=16Hz), 8.52 (1H, d, J=16Hz), 8.60 (2H, d, J=6Hz)

(4) 4-[3-(4-Acetyloxy-3-methoxyphenyl)propenoyl]-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydro-imidazo[1,2-b][1,2,4]triazine

mp : 172-178°C

IR (Nujol) : 3270, 1765, 1660, 1605, 1540, 1515, 1220, 1200 cm^{-1}

NMR ($CDCl_3$, δ) : 2.32 (3H, s), 3.47 (2H, m), 3.77 (3H, s), 4.01 (2H, t, J=5Hz), 4.78 (1H, t, J=6Hz), 6.97 (2H, t, J=9Hz), 7.01 (1H, d, J=8Hz), 7.10 (1H, d, J=8Hz), 7.22 (1H, s), 7.39 (2H, d, J=6Hz), 7.50 (2H, dd, J=5Hz, 9Hz), 7.75 (1H, d, J=16Hz), 8.60 (2H, d, J=6Hz), 8.63 (1H, d, J=16Hz)

(5) 6-(4-Fluorophenyl)-4-(3-phenylpropenoyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 235-236°C

IR (Nujol) : 1665, 1620, 1610, 1540, 1355, 1210 cm^{-1}

NMR ($CDCl_3$, δ) : 3.46 (2H, t, J=5Hz), 4.07 (2H, t, J=5Hz), 7.01 (2H, t, J=9Hz), 7.35-7.45 (5H, m), 7.51 (2H, dd, J=5Hz, 9Hz), 7.60 (2H, m), 7.83 (1H, d, J=16Hz), 8.52 (1H, d, J=16Hz), 8.55 (2H, d, J=5Hz)

(6) 4-[4-(5-Chloro-2-methoxyphenyl)butanoyl]-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydro-imidazo[1,2-b][1,2,4]triazine

mp : 90-93°C

IR (Nujol) : 3200, 1675, 1605, 1550, 1540, 1495,

1250, 1220 cm^{-1}

NMR ($CDCl_3$, δ) : 2.06 (2H, tt, J=7Hz, 7Hz), 2.70 (2H, t, J=7Hz), 3.26 (2H, t, J=7Hz), 3.43 (2H, q, J=5Hz), 3.74 (3H, s), 3.97 (2H, t, J=5Hz), 4.49 (1H, t, J=5Hz), 6.72 (1H, d, J=9Hz), 7.02 (2H, t, J=9Hz), 7.05-7.17 (2H, m), 7.40-7.55 (4H, m), 8.56 (2H, d, J=6Hz)

(7) 4-[3-(3,4-Diacetyloxyphenyl)propenoyl]-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 177-180°C

IR (Nujol) : 3270, 1775 (sh), 1765, 1660, 1625, 1600, 1550, 1505, 1350, 1210, 1200, 1180 cm^{-1}

NMR ($CDCl_3$, δ) : 2.29 (3H, s), 2.32 (3H, s), 3.45 (2H, m), 4.02 (2H, t, J=6Hz), 5.08 (1H, t, J=7Hz), 7.00 (2H, t, J=9Hz), 7.19 (1H, d, J=8Hz), 7.45-7.55 (6H, m), 7.71 (1H, d, J=16Hz), 8.53 (1H, d, J=16Hz), 8.55 (2H, d, J=5Hz)

(8) 6-(4-Fluorophenyl)-4-nonanoyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine dihydrochloride

mp : 230-234°C

IR (Nujol) : 3150, 2550, 1670, 1630, 1545, 1500 cm^{-1}

NMR (CD_3OD, δ) : 0.89 (3H, t, J=7Hz), 1.15-1.50 (10H, m), 1.73 (2H, m), 3.16 (2H, t, J=7Hz), 3.43 (2H, t, J=5Hz), 3.97 (2H, t, J=5Hz), 7.16 (2H, t, J=9Hz), 7.58 (2H, dd, J=5Hz, 9Hz), 7.99 (2H, d, J=6Hz), 8.62 (2H, d, J=6Hz)

(9) 4-Phenylsulfonyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 225-226°C

IR (Nujol) : 1550, 1342, 1185, 1170, 1155 cm^{-1}

NMR (CD_3OD, δ) : 3.29 (2H, t, J=5Hz), 4.02 (2H, t, J=5Hz), 7.00 (2H, t, J=9Hz), 7.35 (2H, d, J=6Hz), 7.41 (2H, dd, J=5Hz, 9Hz), 7.50-7.80 (3H, m), 8.17 (2H, d, J=8Hz), 8.45 (2H, d, J=6Hz)

(10) 6-(4-Fluorophenyl)-7-(pyridin-4-yl)-4-(4-trifluoromethylphenylsulfonyl)-1,2,3,4-trtrahydro-imidazo[1,2-b][1,2,4]triazine

mp : 249.5-250.5°C

IR (Nujol) : 3160, 1595, 1520, 1325, 1230, 1175, 1125, 825 cm^{-1}

NMR ($CDCl_3$, δ) : 3.43 (2H, q, J=6Hz), 4.03 (2H, t, J=6Hz), 4.90 (1H, t, J=6Hz), 6.97 (2H, t, J=9Hz), 7.28 (2H, d, J=6Hz), 7.39 (2H, dd, J=5Hz, 9Hz), 7.84 (2H, d, J=8Hz), 8.40 (2H, d, J=8Hz), 8.52 (2H, br)

(11) 6-(4-Fluorophenyl)-4-morpholinocarbonyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 204-205°C

IR (Nujol) : 3230, 1635, 1540, 1420, 1242, 1110 cm^{-1}

NMR ($CDCl_3$, δ) : 3.40-3.70 (6H, m), 3.75-3.90 (6H, m), 4.84 (1H, t, J=6Hz), 6.98 (2H, t, J=9Hz), 7.37 (2H, d, J=6Hz), 7.43 (2H, dd, J=5Hz, 9Hz), 8.53 (2H, d, J=6Hz)

(12) 4-Cyclohexylcarbonyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 189-190°C

IR (Nujol) : 3240, 1632, 1600, 1530, 1202, 830 cm^{-1}

NMR ($CDCl_3$, δ) : 1.10-2.15 (11H, m), 3.45 (2H, q, J=6Hz), 3.94 (2H, t, J=6Hz), 4.79 (1H, t, J=6Hz), 7.00 (2H, t, J=9Hz), 7.42 (2H, d, J=6Hz), 7.50 (2H, dd, J=5Hz, 9Hz), 8.59 (2H, d, J=6Hz)

(13) 6-(4-Fluorophenyl)-7-(pyridin-4-yl)-4-nicotinoyl-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 224-225°C
IR (Nujol) : 3160, 1660, 1597, 1535, 1330 cm^{-1}
NMR ($CDCl_3$, δ) : 3.58 (2H, q, J=6Hz), 4.15 (2H, t, J=6Hz), 5.20 (1H, t, J=6Hz), 6.84 (2H, t, J=9Hz), 7.06 (2H, dd, J=5Hz, 9Hz), 7.30-7.50 (3H, m), 7.97 (1H, d, J=7Hz), 8.55 (2H, d, J=6Hz), 8.71 (1H, d, J=5Hz), 8.76 (1H, s)

(14) 6-(4-Fluorophenyl)-4-methoxyacetyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 181.5-183°C
IR (Nujol) : 3250, 1690, 1670, 1600, 1550, 1240, 1215, 1120, 845 cm^{-1}
NMR ($CDCl_3$, δ) : 3.42-3.54 (2H, m), 3.55 (3H, s), 4.05 (2H, t, J=6Hz), 4.92 (2H, s), 4.93 (1H, br), 7.01 (2H, t, J=9Hz), 7.42 (2H, d, J=6Hz), 7.48 (2H, dd, J=5Hz, 9Hz), 8.40 (2H, d, J=6Hz)

(15) 6-(4-Fluorophenyl)-7-(pyridin-4-yl)-4-(2-thienylcarbonyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 188-189°C
IR (Nujol) : 3190, 1635, 1600, 1550, 1540, 1350, 1300, 1250, 1210, 1160, 1065, 995, 840, 820, 740 cm^{-1}
NMR ($CDCl_3$, δ) : 3.52 (2H, q, J=6Hz), 4.25 (2H, t, J=6Hz), 5.32 (1H, t, J=6Hz), 6.95 (2H, t, J=9Hz), 7.05 (1H, t, J=5Hz), 7.32 (2H, dd, J=5Hz, 9Hz), 7.48 (2H, dd, J=1Hz, 6Hz), 7.57 (1H, d, J=5Hz), 7.77 (1H, d, J=5Hz), 8.56 (2H, dd, J=1Hz, 6Hz)

(16) 6-(4-Fluorophenyl)-7-(pyridin-4-yl)-4-(2,2,2-tri-

fluoroethylsulfonyl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine

mp : 113-115°C

IR (Nujol) : 3680, 3200, 1540, 1515, 1410, 1320, 1255, 1165, 1090, 1020, 840, 715 cm^{-1}

NMR ($CDCl_3$, δ) : 3.47-3.57 (2H, m), 4.00 (2H, t, J=5Hz), 4.71-4.90 (3H, m), 6.98 (2H, t, J=9Hz), 7.37 (2H, d, J=5Hz), 7.42 (2H, dd, J=5Hz, 9Hz), 8.60 (2H, d, J=5Hz)

Example 7

(1) To 1,4-diacetyl-7-(1,4-dihydro-1-ethoxycarbonyl-pyridin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (100 mg) was added 0.435M sodium ethoxide in ethanol (1.1 ml). After stirring for 2.5 hours at ambient temperature under nitrogen, the mixture was poured into ice-cold water (22 ml). The solid was collected, washed with water and dried. The solid was recrystallized from a mixture of ethanol and diethyl ether to yield 7-(1,4-dihydro-1-ethoxycarbonylpyridin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (60 mg).

mp : 185-186.5°C

IR (Nujol) : 3230, 1710, 1690, 1620, 1505, 1330, 1310, 1210, 1200, 1120, 975, 935, 840 cm^{-1}

NMR (DMSO-d_6, δ) : 1.27 (3H, t, J=7Hz), 3.02-3.13 (2H, m), 3.16-3.28 (2H, m), 4.14 (2H, q, J=7Hz), 4.52 (1H, m), 4.75-4.90 (2H, br), 5.93 (1H, t, J=7Hz), 6.53 (1H, m), 6.75 (2H, d, J=8Hz), 7.03 (2H, t, J=9Hz), 7.45 (2H, dd, J=5Hz, 9Hz)

The following compounds were obtained according to a similar manner to that of Example 7-(1).

(2) 6-(4-Fluoro-1-naphthyl)-7-(pyridin-4-yl)-1,2,3,4-

tetrahyroimidazo[1,2-b][1,2,4]triazine
mp : 229.5-230.5°C
IR (Nujol) : 3180, 3080, 1610, 1595, 1360, 1330, 1235, 1050, 820, 760, 690 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 10:1, δ) : 3.48-3.62 (4H, m), 7.13 (1H, m), 7.16 (2H, d, J=6Hz), 7.35 (1H, dd, J=5Hz, 9Hz), 7.45 (1H, t, J=8Hz), 7.56 (1H, t, J=8Hz), 7.86 (1H, d, J=8Hz), 8.15 (1H, d, J=8Hz), 8.22 (2H, d, J=6Hz)

(3) 6-(4-Ethoxycarbonylphenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 222-223.5°C
IR (Nujol) : 3590, 3250, 1710, 1690, 1630, 1500, 1280, 1110, 780 cm^{-1}
NMR (DMSO-d_6, δ) : 1.28 (3H, t, J=7Hz), 2.98-3.13 (2H, br), 3.23-3.37 (2H, br), 4.30 (2H, q, J=7Hz), 6.35 (1H, t, J=7Hz), 7.05 (1H, s), 7.33 (2H, d, J=5Hz), 7.55 (2H, d, J=9Hz), 7.83 (2H, d, J=9Hz), 8.50 (2H, d, J=5Hz)

(4) 6-(4-Fluorophenyl)-7-(3-methoxycarbonylpyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 350.5-352°C (dec.)
IR (Nujol) : 3130, 1650, 1635, 1590, 1560, 1510, 1440, 1230, 1200, 940, 835 cm^{-1}
NMR ($CDCl_3$:CD_3OD = 7:1, δ) : 3.70 (2H, t, J=5Hz), 3.81 (3H, s), 4.36 (2H, t, J=5Hz), 7.23 (2H, t, J=9Hz), 7.45 (1H, d, J=6Hz), 7.63 (2H, dd, J=5Hz, 9Hz), 8.46 (1H, d, J=6Hz), 9.26 (1H, s)

Example 8

A solution of 1,4-diacetyl-6-(4-ethoxycarbonylphenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (60 mg) in 4%

methanolic sodium hydroxide solution (2.08 ml) was stirred for 2.5 hours at ambient temperature. To the resulting mixture was added 10% aqueous sodium hydroxide solution in one portion at the same temperature. After stirring for 1 hour at ambient temperature, the mixture was neutralized with 1N hydrochloric acid and the solvents were removed in vacuo. The residue was dissolved in 1N hydrochloric acid and the solution was neutralized with aqueous solution saturated with sodium bicarbonate. The separated solid was collected, washed with water and dried to yield 6-(4-carboxyphenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (37 mg).

mp : 270-272°C

IR (Nujol) : 3230, 1630, 1600, 1540, 1505, 1340, 1325, 1250, 1205, 840, 790 cm^{-1}

NMR (DMSO-d_6, δ) : 2.99-3.15 (2H, br), 3.28-3.44 (2H, br), 6.34 (1H, t, J=7Hz), 7.03 (1H, br s), 7.34 (2H, d, J=6Hz), 7.52 (2H, d, J=9Hz), 7.82 (2H, d, J=9Hz), 8.49 (2H, d, J=6Hz)

Example 9

To a solution of 1,4-diacetyl-6-(4-ethoxycarbonylphenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine (101.5 mg) in dry tetrahydrofuran (4 ml) was added lithium aluminumhydride (44.4 mg) dropwise at 0°C in an atmosphere of nitrogen. After the mixture was stirred for 30 minutes at the same temperature, ice and aqueous 1N sodium hydroxide solution were added to the reaction mixture. The aqueous solution was extracted with 10% methanol in dichloromethane, and the extract was washed with brine and dried over anhydrous sodium sulfate. The solution was concentrated in vacuo and the residue was purified by column chromatography on silica gel (dichloromethane:methanol = 98:2 as eluent) to give a solid which was crystallized from a mixture of

methanol and diethyl ether to yield 6-(4-hydroxymethylphenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (39 mg)

mp : 255.5-258°C

IR (Nujol) : 3400, 3200, 3070, 1630, 1590, 1330, 1250, 1080, 1005, 830 cm^{-1}

NMR (DMSO-d_6, δ) : 2.98-3.12 (2H, br), 3.24-3.38 (2H, br), 4.45 (2H, d, J=5Hz), 5.15 (1H, t, J=5Hz), 6.33 (1H, t, J=7Hz), 6.97 (1H, br s), 7.22 (2H, d, J=9Hz), 7.31 (2H, d, J=6Hz), 7.37 (2H, d, J=9Hz), 8.43 (2H, d, J=6Hz)

Example 10

To a mixture of 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (118.1 mg) and N,N-dimethylglycine (123.7 mg) in N,N-dimethylformamide (9.4 ml) was added 3-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (230 mg). The mixture was stirred for 2 days at ambient temperature and then concentrated in vacuo. The residue was partitioned between dichloromethane and water. The aqueous layer was extracted twice with dichloromethane . The combined organic layers were washed with an aqueous solution saturated with sodium bicarbonate and brine successively, and dried over anhydrous sodium sulfate. The solution was concentrated in vacuo, and the residue was purified by thin layer chromatography on silica gel to give a solid which was crystallized from a mixture of diethyl ether and diisopropyl ether to yield (4-(N,N-dimethylaminoacetyl)-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (15.0 mg).

mp : 181.5-183.5°C

IR (Nujol) : 3160, 1680, 1600, 1550, 1220, 1210, 1050, 1000, 840 cm^{-1}

NMR ($CDCl_3$, δ) : 2.60 (6H, s), 3.34-3.47 (2H, m), 4.00 (2H, t, J=5Hz), 4.26 (2H, s), 5.42 (1H, t, J=7Hz), 6.99 (2H, t, J=9Hz), 7.36 (2H, dd, J=1Hz, 6Hz), 7.46 (2H, dd, J=5Hz, 9Hz), 8.61 (2H, dd, J=1Hz, 6Hz)

Example 11

A mixture of 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (236.6 mg) and ethyl isocyanate (200 µl) in chloroform (16 ml) was refluxed for 4 hours in an atmosphere of nitrogen. The reaction mixture was concentrated in vacuo, the oily residue was purified by column chromatography on silica gel (eluted with 1-3% methanol in dichloromethane) to yield 1,4-bis(ethylcarbamoyl)-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]-triazine (150 mg) and 4-ethylcarbamoyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]-triazine (15.2 mg) and 1-ethylcarbamoyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine (61.3 mg).

- 1,4-Bis(ethylcarbamoyl)-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
  mp : 196.5-198°C
  IR (Nujol) : 3380, 3250, 1690, 1555, 1510, 1210, 840 cm^{-1}

- 4-Ethylcarbamoyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
  mp : 213.5-214.5°C
  IR (Nujol) : 3220, 1665, 1600, 1570, 1545, 1515, 1230, 850 cm^{-1}
  NMR ($CDCl_3$, δ) : 1.27 (3H, t, J=7Hz), 3.37-3.52 (4H, m), 4.00 (2H, t, J=5Hz), 4.74 (1H, t, J=7Hz),

7.00 (2H, t, J=9Hz), 7.36-7.48 (4H, m), 8.58 (2H, d, J=5Hz), 9.62 (1H, t, J=5Hz)

- 1-Ethylcarbamoyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

  mp : 202.5-203.5°C

  IR (Nujol) : 3320, 3200, 1685, 1635, 1600, 1510, 1250, 1210, 840, 820 cm^{-1}

  NMR ($CDCl_3$, δ) : 0.73 (3H, t, J=7Hz), 2.82-3.36 (3H, m), 3.37-3.52 (2H, m), 4.70 (1H, br), 5.02 (1H, t, J=6Hz), 6.95-7.10 (3H, m), 7.32 (2H, d, J=6Hz), 7.46 (2H, dd, J=5Hz, 9Hz), 8.52 (2H, d, J=6Hz)

Example 12

(1) To a suspension of 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (100 mg) in methanol (2 ml) was added 8N-methanolic hydrogen chloride (3 ml) in one portion. The resulting clear solution was concentrated in vacuo. To the residue was added ethanol (5 ml) and the solution was concentrated in vacuo. The residue was crystallized from acetonitrile and recrystallized from a mixture of ethanol and acetonitrile to give 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine dihydrochloride (105 mg) as yellow crystals.

mp : 184-186°C

IR (Nujol) : 3230, 3190, 3050, 2650 (br), 1682, 1630, 1600, 1500, 1230, 1200, 860, 835, 815 cm^{-1}

NMR (CD_3OD, δ) : 3.43 (2H, t, J=5Hz), 3.60 (2H, t, J=5Hz), 7.29 (2H, t, J=9Hz), 7.56 (2H, dd, J=5Hz, 9Hz), 8.11 (2H, d, J=6Hz), 8.78 (2H, d, J=6Hz)

The following compound was obtained according to a

similar manner to that of Example 12-(1).

(2) 6-(5-Chlorothiophen-2-yl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine dihydrochloride

mp : 180-187°C

IR (Nujol) : 3400, 3150, 3050, 2680, 1695, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 3.18 (2H, t, J=5Hz), 3.40 (2H, t, J=5Hz), 7.20 (1H, d, J=4Hz), 7.38 (1H, d, J=4Hz), 8.07 (2H, d, J=6Hz), 8.87 (2H, d, J=6Hz)

Example 13

To a suspension of 4-[3-(4-acetyloxy-3-methoxyphenyl)propenoyl]-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (110 mg) in methanol (10 ml) was added sodium bicarbonate (110 mg). After stirring for 6 hours at ambient temperature, the mixture was poured into water. The solid was collected, washed with water and methanol and dried to yield 6-(4-fluorophenyl)-4-[3-(4-hydroxy-3-methoxyphenyl)-propenoyl]-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine (71 mg).

mp : >250°C

IR (Nujol) : 3240, 1655, 1600, 1535 cm^{-1}

NMR (DMSO-d_6, δ) : 3.32 (2H, m), 3.78 (3H, s), 3.91 (2H, t, J=5Hz), 6.61 (1H, t, J=6Hz), 6.83 (1H, d, J=8Hz), 7.12 (2H, t, J=9Hz), 7.18 (1H, d, J=8Hz), 7.25 (1H, s), 7.42 (2H, d, J=5Hz), 7.54 (2H, dd, J=5Hz, 9Hz), 7.63 (1H, d, J=16Hz), 8.55 (1H, d, J=16Hz), 8.61 (2H, d, J=5Hz)

Example 14

(1) A mixture of 6-(4-fluorophenyl)-7-[(pyridin-4-yl)-thio]imidazo[1,2-b][1,2,4]triazine (97 mg) and sodium borohydride (18 mg) in anhydrous ethanol (5 ml) was heated

under reflux for 20 minutes. After cooling, the reaction mixture was poured into ice-water. The separated solid was collected, washed with water and dried. Recrystallization from ethanol gave 6-(4-fluorophenyl)-7-[(pyridin-4-yl)thio]-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (35 mg).

mp : 203-205°C

IR (Nujol) : 3200, 3120, 1610, 1575, 1480 cm^{-1}

NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 3.25 (2H, t, J=5Hz), 3.48 (2H, t, J=5Hz), 7.04 (2H, t, J=9Hz), 7.11 (2H, d, J=6Hz), 7.74 (2H, dd, J=5Hz, 9Hz), 8.30 (2H, d, J=6Hz)

The following compounds were obtained according to a similar manner to that of Example 14-(1).

(2) 6-(4-Fluorophenyl)-7-[(pyridin-4-yl)sulfinyl]-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 210-215°C (dec.)

IR (Nujol) : 3230, 3060, 1625, 1490, 1245, 1215, 840, 820 cm^{-1}

NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 3.25 (2H, t, J=5Hz), 3.49 (2H, t, J=5Hz), 7.06 (2H, t, J=9Hz), 7.16 (2H, d, J=7Hz), 7.75 (2H, dd, J=5Hz, 9Hz), 8.10 (2H, d, J=7Hz)

(3) 6-(4-Fluorophenyl)-7-(1-methylimidazo-2-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine

mp : 223-224°C

IR (Nujol) : 3170, 3130, 3110, 3070, 1625, 1610, 1525, 1510, 1240, 1225, 1155, 840 cm^{-1}

NMR ($CDCl_3$:CD_3OD = 1:1, δ) : 3.23 (3H, s), 3.27 (2H, t, J=5Hz), 3.46 (2H, t, J=5Hz), 6.98 (2H, t, J=9Hz), 7.00 (1H, s), 7.21 (1H, s), 7.23 (2H, dd, J=5Hz, 9Hz)

(4) 6-(4-Fluorophenyl)-7-[(pyridin-2-yl)methyl]-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine
mp : 183.5-185°C
IR (Nujol) : 1630, 1590, 1510, 1440, 1210, 835 cm^{-1}
NMR (DMSO-d_6, δ) : 3.0-3.14 (2H, m), 3.19-3.30 (2H, m), 4.15 (2H, s), 5.95 (1H, t, J=7Hz), 6.57 (1H, m), 7.10 (2H, t, J=8Hz), 7.16-7.27 (2H, m), 7.58-7.77 (3H, m), 8.51 (1H, d, J=5Hz)

Example 15

A mixture of 6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (207 mg) and methanesulfonyl chloride (0.33 ml) in pyridine (3 ml) was stirred at 50°C for 16 hours. The mixture was concentrated in vacuo and to the residue was added an aqueous saturated sodium bicarbonate solution. The separated oil was extracted with dichloromethane and the extract was washed with brine, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel and the obtained oil was crystallized from methanol to yield 1,4-bis(methylsulfonyl)-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine (150 mg).

mp : 237-238°C
IR (Nujol) : 1560, 1508, 1350, 1320, 1220, 1165, 960, 795 cm^{-1}
NMR (CD_3OD, δ) : 2.64 (3H, s), 3.51 (3H, s), 3.87 (1H, dt, J=5Hz, 15Hz), 4.10-4.18 (2H, m), 4.60 (1H, dd, J=4Hz, 15Hz), 7.04 (2H, t, J=9Hz), 7.43 (2H, d, J=5Hz), 7.48 (2H, dd, J=5Hz, 9Hz), 8.60 (2H, d, J=5Hz)

Example 16

A mixture of 4-acetyl-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (210

mg) and methanesulfonyl chloride (0.25 ml) in pyridine (3 ml) was stirred at ambient temperature for 2 days. The mixture was concentrated in vacuo and to the residue was added an aqueous saturated sodium bicarbonate solution. The separated oil was extracted with ethyl acetate and the extract was washed with brine, dried and concentrated in vacuo. The obtained oil was crystallized from methanol to yield 4-acetyl-6-(4-fluorophenyl)-1-methylsulfonyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine (160 mg).

mp : 188-189°C

IR (Nujol) : 1685, 1560, 1440, 1345, 1155, 835, 800 cm^{-1}

NMR ($CDCl_3$, δ) : 2.48 (3H, s), 2.80 (3H, s), 3.69 (1H, m), 4.00-4.25 (2H, m), 4.62 (1H, dd, J=6Hz, 15Hz), 7.02 (2H, t, J=9Hz), 7.37 (2H, d, J=6Hz), 7.44 (2H, dd, J=5Hz, 9Hz), 8.07 (2H, d, J=6Hz)

Example 17

A suspension of 4-acetyl-6-(4-fluorophenyl)-1-methylsulfonyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo-[1,2-b][1,2,4]triazine (148 mg) in 4% methanolic sodium hydroxide (5 ml) was stirred for 2 hours at ambient temperature and to the mixture was added ice-cold water. The separated solid was collected, washed with water and dried. The obtained solid was recrystallized from diethyl ether to yield 6-(4-fluorophenyl)-1-methylsulfonyl-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]-triazine (32 mg).

mp : 162-163°C (dec.)

IR (Nujol) : 3330, 1660, 1600, 1315, 1295, 1280, 1240, 1150, 1125, 1110, 965, 845 cm^{-1}

NMR ($CDCl_3$, δ) : 2.88 (3H, s), 3.40 (2H, t, J=5Hz), 3.68 (2H, t, J=5Hz), 7.07 (2H, t, J=9Hz), 7.28 (2H, d, J=5Hz), 8.02 (2H, dd, J=6Hz, 9Hz), 8.53

(2H, d, J=5Hz)

Example 18

4-(2-Carboxybenzoyl)-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine was obtained by reacting 6-(4-fluorophenyl)-7-(pyridine-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine with phthalic anhydride.

mp : 131-133°C

IR (Nujol) : 3400, 3200, 1665, 1640, 1550, 1515, 1340, 1225, 1155, 1060, 835 cm^{-1}

NMR (DMSO-d_6, δ) : 3.37-3.46 (2H, m), 3.94-4.07 (2H, m), 6.67 (1H, t, J=7Hz), 6.95 (4H, d, J=8Hz), 7.33 (2H, d, J=6Hz), 7.39 (1H, d, J=7Hz), 7.52-7.71 (2H, m), 7.98 (1H, d, J=7Hz), 8.56 (2H, d, J=6Hz)

Example 19

7-(3-Carboxypyridin-4-yl)-6-(4-fluorophenyl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine was obtained by treating 7-(3-methoxycarbonylpyridin-4-yl)-6-(4-fluorophenyl)-1,4-diacetyl-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]triazine according to a similar manner to that of Example 8.

mp : >360°C

IR (Nujol) : 3250, 1600, 1510, 1215, 1155, 840, 810 cm^{-1}

NMR (DMSO-d_6, δ) : 2.83-3.00 (2H, br), 3.19-3.32 (2H, br), 6.52 (1H, m), 6.68 (1H, br), 6.93-7.03 (3H, m), 7.28 (2H, dd, J=5Hz, 9Hz), 8.30 (1H, d, J=6Hz), 8.80 (1H, m)

Example 20

4-[3-(3,4-Dihydroxyphenyl)propenoyl]-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo-

[1,2-b][1,2,4]triazine was obtained by treating 4-[3-(3,4-diacetoxyphenyl)propenoyl]-6-(4-fluorophenyl)-7-(pyridin-4-yl)-1,2,3,4-tetrahydroimidazo[1,2-b][1,2,4]-triazine according to a similar manner to that of Example 13.

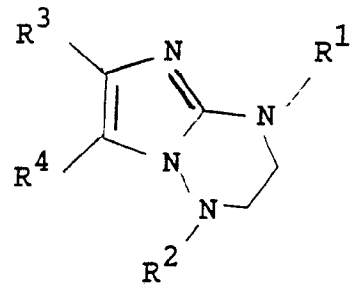
mp : >250°C

IR (Nujol) : 3450, 3270, 3120, 1660, 1610, 1600, 1530, 1520, 1295 cm^{-1}

NMR (DMSO-d_6, δ) : 3.32 (2H, m), 3.90 (2H, m), 6.59 (1H, t, J=6Hz), 6.80 (1H, d, J=8Hz), 6.98 (1H, d, J=8Hz), 7.07 (1H, s), 7.18 (2H, t, J=9Hz), 7.41 (2H, d, J=6Hz), 7.50-7.65 (3H, m), 8.32 (1H, d, J=16Hz), 8.60 (2H, d, J=5Hz)

C L A I M S

1. A compound of the formula :



wherein R^1 is hydrogen, lower alkyl or acyl,
R^2 is hydrogen, or acyl,
R^3 is aryl which may have suitable substituent(s), or heterocyclic group which may have suitable substituent(s), and
R^4 is heterocyclic group which may have suitable substituent(s), heterocyclic(lower)alkyl, heterocyclicthio, or heterocyclicsulfinyl,
and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein
R^1 is hydrogen, lower alkyl, lower or higher alkanoyl which may have one to five suitable substituent(s),
carbamoyl which may have one or two suitable substituent(s),
lower alkylsulfonyl which may have one to three suitable substituent(s),
arylsulfonyl which may have one to three suitable substituent(s),

arylcarbonyl which may have one to three suitable substituent(s),
cyclo(lower)alkylcarbonyl,
ar(lower)alkanoyl which may have one to three suitable substituent(s),
ar(lower)alkenoyl which may have one to three suitable substituent(s), or
heterocycliccarbonyl,

R^2 is hydrogen,
lower or higher alkanoyl, carbamoyl which may have one or two suitable substituent(s), or
lower alkylsulfonyl,

R^3 is aryl which may have one to three substituent(s) selected from the group consisting of halogen,
mono(or di or tri)halo(lower)alkyl,
hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, carboxy, protected carboxy and mono(or di or tri)haloaryl; or
heterocyclic group which may have one to three suitable substituent(s), and

R^4 is heterocyclic group which may have one to three substituent(s) selected from the group consisting of protected carboxy, carboxy, halogen and lower alkyl;
unsaturated 5 or 6-membered heteromonocyclic-(lower)alkyl in which heteromonocyclic group contains 1 to 4 nitrogen atom(s),
unsaturated 5 or 6-membered heteromonocyclicthio in which heteromonocyclic group contains 1 to 4 nitrogen atom(s), or
unsaturated 5 or 6-membered heteromonocyclic-sulfinyl in which heteromonocyclic group contains 1 to 4 nitrogen atom(s).

3. A compound of claim 2, wherein

R^1 is hydrogen, lower alkyl, lower or higher alkanoyl which may have one to five substituent(s) selected from the group consisting of halogen, lower alkoxy and N,N-di(lower)alkylamino, mono(or di)lower alkylcarbamoyl, lower alkylsulfonyl which may have one to three halogen, arylsulfonyl which may have mono(or di or tri)halo(lower)alkyl, arylcarbonyl which may have one or two substituent(s) selected from the group consisting of carboxy and protected carboxy, cyclo(C_5-C_6)alkylcarbonyl, ar(lower)alkanoyl which may have one or two substituent(s) selected from the group consisting of lower alkoxy and halogen, ar(lower)alkenoyl which may have one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, hydroxy and protected hydroxy, unsaturated 5 or 6-membered heteromonocycliccarbonyl in which heteromonocyclic group contains 1 to 4 nitrogen atom(s), saturated 5 or 6-membered heteromonocycliccarbonyl in which heteromonocyclic group contains 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), or unsaturated 5 or 6-membered heteromonocycliccarbonyl in which heteromonocyclic group contains 1 to 2 sulfur atom(s),

R^2 is hydrogen, lower alkanoyl, mono(or di)lower alkylcarbamoyl, or lower alkylsulfonyl,

R^3 is aryl which may have one or two substituent(s) selected from the group consisting of halogen,

mono(or di or tri)halo(lower)alkyl, hydroxy(lower)alkyl, protected hydroxy(lower)alkyl, carboxy, protected carboxy and mono(or di or tri)haloaryl,
unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 2 sulfur atom(s) which may have one or two substituent(s) selected from the group consisting of lower alkyl and halogen, or
unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) which may have lower alkyl, and

R^4 is unsaturated 5 or 6-membered heteromonocyclic group containing 1 to 4 nitrogen atom(s) which may have one to three substituent(s) selected from the group consisting of protected carboxy, carboxy, halogen and lower alkyl, or
unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s) which may have one to three substituent(s) selected from the group consisting of protected carboxy, carboxy, halogen and lower alkyl,
pyridyl(lower)alkyl,
pyridylthio or pyridylsulfinyl.

4. A compound of claim 3 wherein

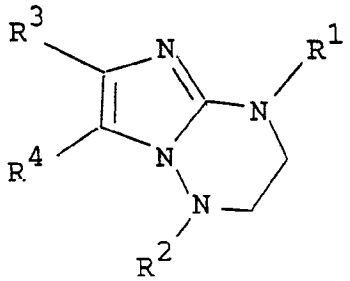
R^1 is hydrogen, lower alkyl, C_1-C_{10} alkanoyl which may have one to five substituent(s) selected from the group consisting of halogen, lower alkoxy and N,N-di(lower)alkylamino,
mono(or di)lower alkylcarbamoyl, lower alkylsulfonyl which may have one to three halogen,
phenylsulfonyl which may have mono(or di or tri)halo(lower)alkyl,
phenylcarbonyl which may have carboxy or protected carboxy, cyclo(C_5-C_6)alkylcarbonyl,

phenyl(lower)alkanoyl which may have one or two substituent(s) selected from the group consisting of lower alkoxy and halogen, phenyl(lower)alkenoyl which may have one to three substituent(s) selected from the group consisting of lower alkyl, lower alkoxy, hydroxy and protected hydroxy, pyridylcarbonyl, morpholinylcarbonyl or thienylcarbonyl,

R^3 is mono(or di or tri)halophenyl, mono(or di or tri)halonaphthyl, mono(or di or tri)halo(lower)alkylphenyl, hydroxy(lower)alkylphenyl, carboxyphenyl, protected carboxyphenyl, mono(or di or tri)halobiphenylyl, thienyl which may have lower alkyl or halogen, or benzothienyl which may have lower alkyl, and

R^4 is dihydropyridyl, pyridyl, quinolyl, dihydroquinolyl or imidazolyl, each of which may have one or two substituent(s) selected from the group consisting of protected carboxy, carboxy, halogen and lower alkyl, pyridyl(lower)alkyl, pyridylthio, or pyridylsulfinyl.

5. A process for preparing a compound of the formula :



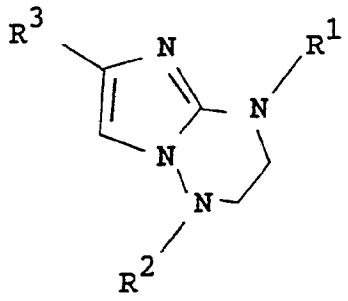
wherein R^1 is hydrogen, lower alkyl or acyl,

R^2 is hydrogen, or acyl,

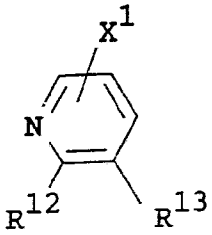
R^3 is aryl which may have suitable substituent(s), or heterocyclic group

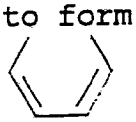
which may have suitable substituent(s),
and
R^4 is heterocyclic group which may have
suitable substituent(s),
heterocyclic(lower)alkyl,
heterocyclicthio,
or heterocyclicsulfinyl,
or a salt thereof,
which comprises,

(1) reacting a compound of the formula :



wherein R^1, R^2 and R^3 are each as defined above,
or a salt thereof with a compound of the formula :

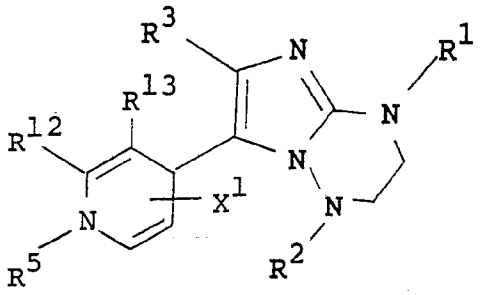


wherein X^1 is an acid residue, carboxy or protected carboxy, and
R^{12} and R^{13} are each hydrogen, or
R^{12} and R^{13} are linked together to form a group of the formula :  ,

or a salt thereof and with a compound of the formula:

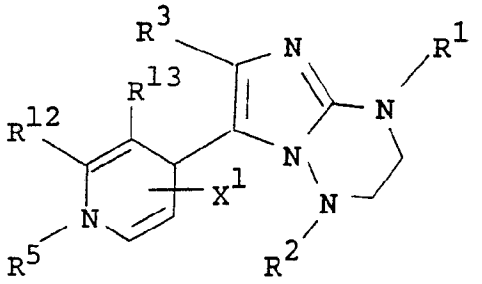
$$X^2 - R^5$$

wherein R^5 is protected carboxy, and
X^2 is an acid residue,
to give a compound of the formula :

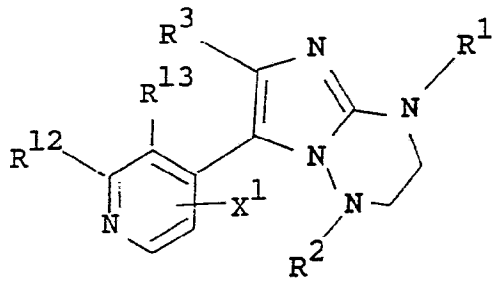


wherein R^1, R^2, R^3, R^5, R^{12}, R^{13} and X^1 are each as defined above,
or a salt thereof, or

(2) subjecting a compound of the formula :



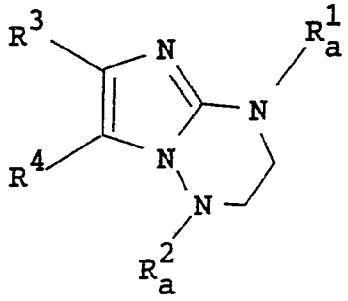
wherein R^1, R^2, R^3, R^5, R^{12}, R^{13} and X^1 are each as defined above,
or a salt thereof to oxidation reaction to give a compound of the formula :



wherein R^1, R^2, R^3, R^{12}, R^{13} and X^1 are each as defined above,

or a salt thereof, or

(3) subjecting a compound of the formula :

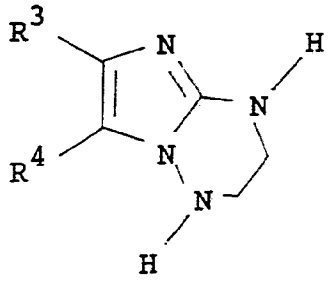


wherein R_a^1 is acyl,

R_a^2 is acyl, and

R^3 and R^4 are each as defined above,

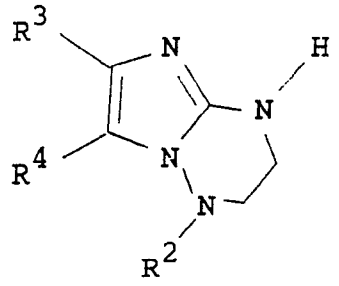
or a salt thereof to deacylation reaction to give a compound of the formula :



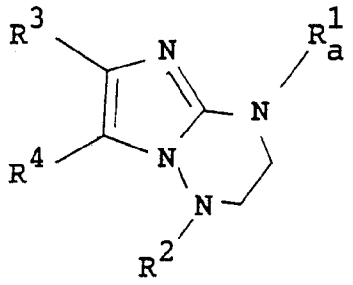
wherein R^3 and R^4 are each as defined above,

or a salt thereof, or

(4) subjecting a compound of the formula :

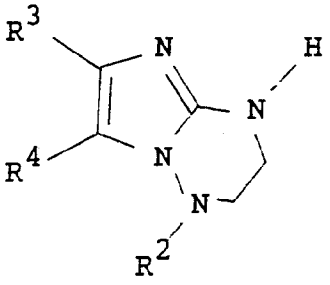


wherein R^2, R^3 and R^4 are each as defined above, or a salt thereof to acylation reaction to give a compound of the formula:



wherein R^1_a, R^2, R^3 and R^4 are each as defined above, or a salt thereof, or

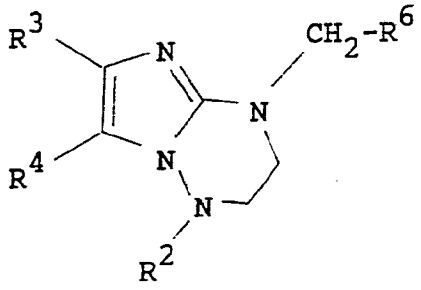
(5) reacting a compound of the formula :



wherein R^2, R^3 and R^4 are each as defined above, or a salt thereof with a compound of the formula :

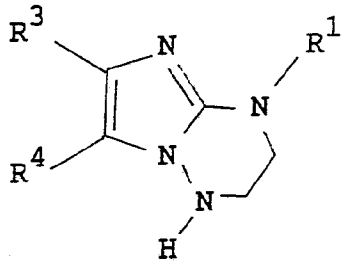
R^6 - CHO

wherein R^6 is hydrogen or C_1-C_5 alkyl,
and then subjecting the resultant compound to reduction reaction to give a compound of the formula:

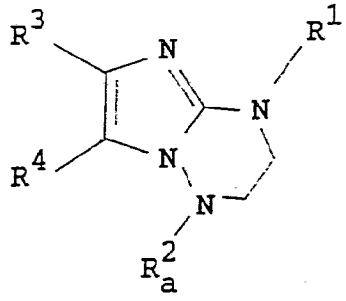


wherein R^2, R^3, R^4 and R^6 are each as defined above, or a salt thereof, or

(6) subjecting a compound of the formula :

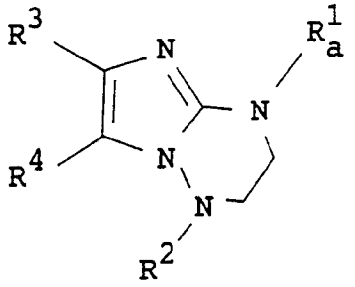


wherein R^1, R^3 and R^4 are each as defined above, or a salt thereof to acylation reaction to give a compound of the formula :

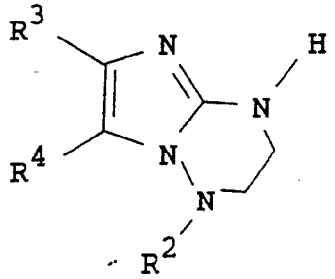


wherein R^1, R^2_a, R^3 and R^4 are each as defined above, or a salt thereof, or

(7) subjecting a compound of the formula :

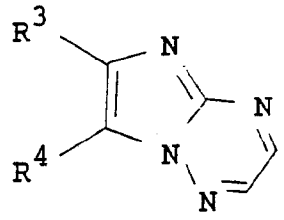


wherein R^1_a, R^2, R^3 and R^4 are each as defined above, or a salt thereof to deacylation reaction to give a compound of the formula :

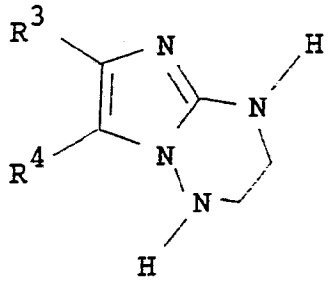


wherein R^2, R^3 and R^4 are each as defined above, or a salt thereof, or

(8) subjecting a compound of the formula :

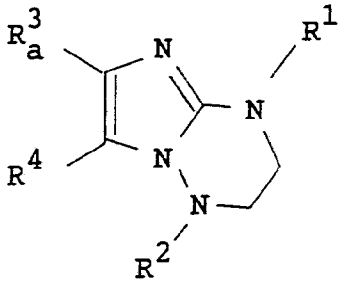


wherein R^3 and R^4 are each as defined above, or a salt thereof to reduction reaction to give a compound of the formula :

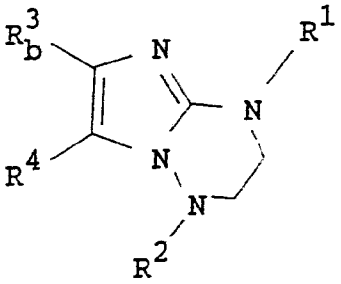


wherein R^3 and R^4 are each as defined above, or a salt thereof, or

(9) subjecting a compound of the formula :

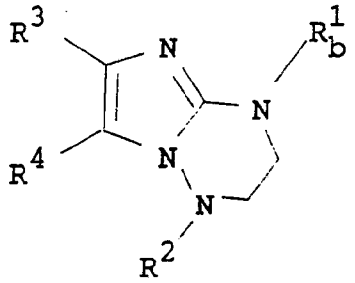


wherein R^1, R^2 and R^4 are each as defined above, and R^3_a is aryl having protected carboxy group(s) or a salt thereof to elimination reaction of the carboxy protective group(s) to give a compound of the formula :

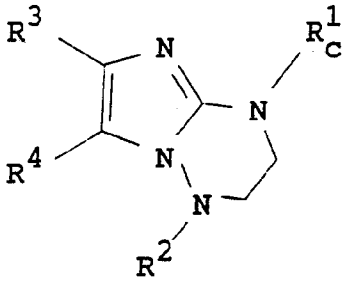


wherein R^1, R^2 and R^4 are each as defined above, and R^3_b is aryl having carboxy group(s), or a salt thereof, or

(10) subjecting a compound of the formula :



wherein R^2, R^3 and R^4 are each as defined above, and R^1_b is acyl having protected hydroxy group(s), or a salt thereof to elimination reaction of the hydroxy protective group(s) to give a compound of the formula :



wherein R^2, R^3 and R^4 are each as defined above, and R^1_c is acyl having hydroxy group(s), or a salt thereof.

6. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

7. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as an inhibitor on the production of Interleukin-1 (IL-1) and an inhibitor on the production of tumor necrosis factor (TNF).

8. A method for the prophylactic or therapeutic treatment of Interleukin-1 (IL-1) and tumor necrosis factor (TNF) mediated diseases which comprises administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

9. A process for preparing a pharmaceutical composition which comprises admixing a compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International Application No PCT/JP 91/01768

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 487/04 A 61 K 31/55 //(C 07 D 487/04
C 07 D 253:00 C 07 D 235:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D A 61 K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
2 A	WO,A,8801169 (SMITHKLINE BECKMAN) 25 February 1988, see claim 1, & US,A,4794114 (cited in the application)	1,6
2 P,A	WO,A,9100092 (SMITHKLINE BEECHAM) 10 January 1991, see claims 1,22	1,6

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19-03-1992	28.04.92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Els Vonk

Form PCT/ISA/210 (second sheet) (January 1985)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND ~~UNSEARCHABLE~~ [1] INCOMPLETELY

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claim numbers 8 because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 8 is directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. JP 9101768

SA 54859

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 08/04/92
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A- 8801169	25-02-88	US-A-	4794114	27-12-88
		AU-A-	7880087	08-03-88
		EP-A-	0321490	28-06-89
		JP-T-	1503782	21-12-89
WO-A- 9100092	10-01-91	AU-A-	6355190	17-01-91
		EP-A-	0411754	06-02-91